

Supplementary information

Genome-wide meta-analysis identifies new susceptibility loci for migraine

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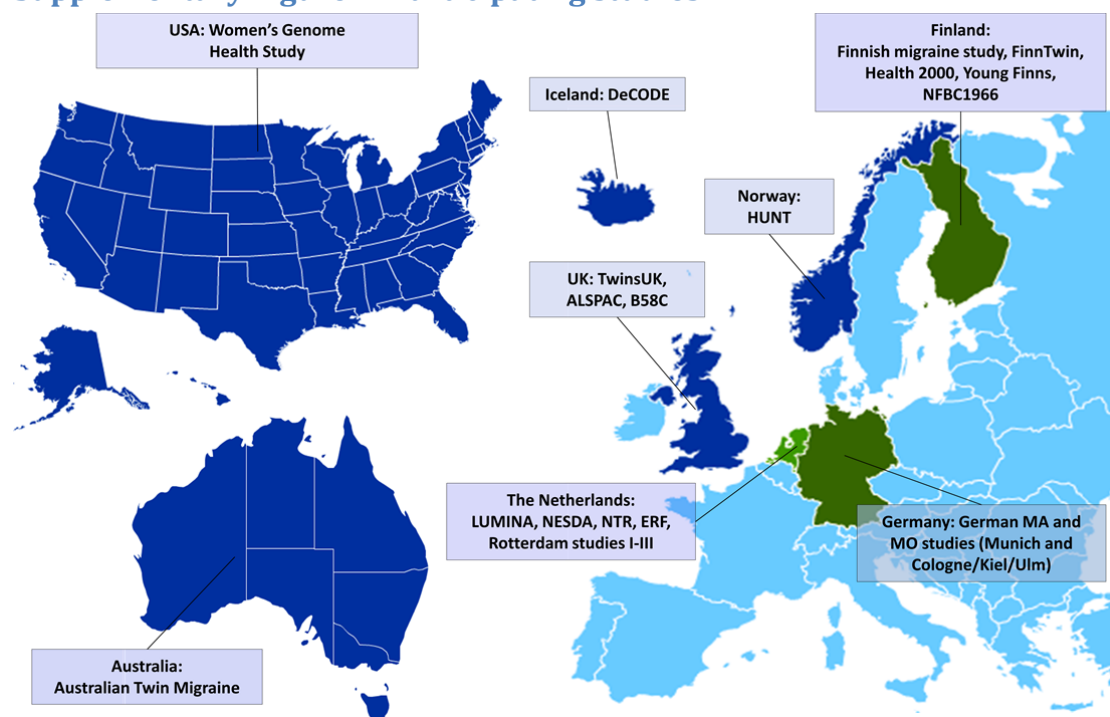
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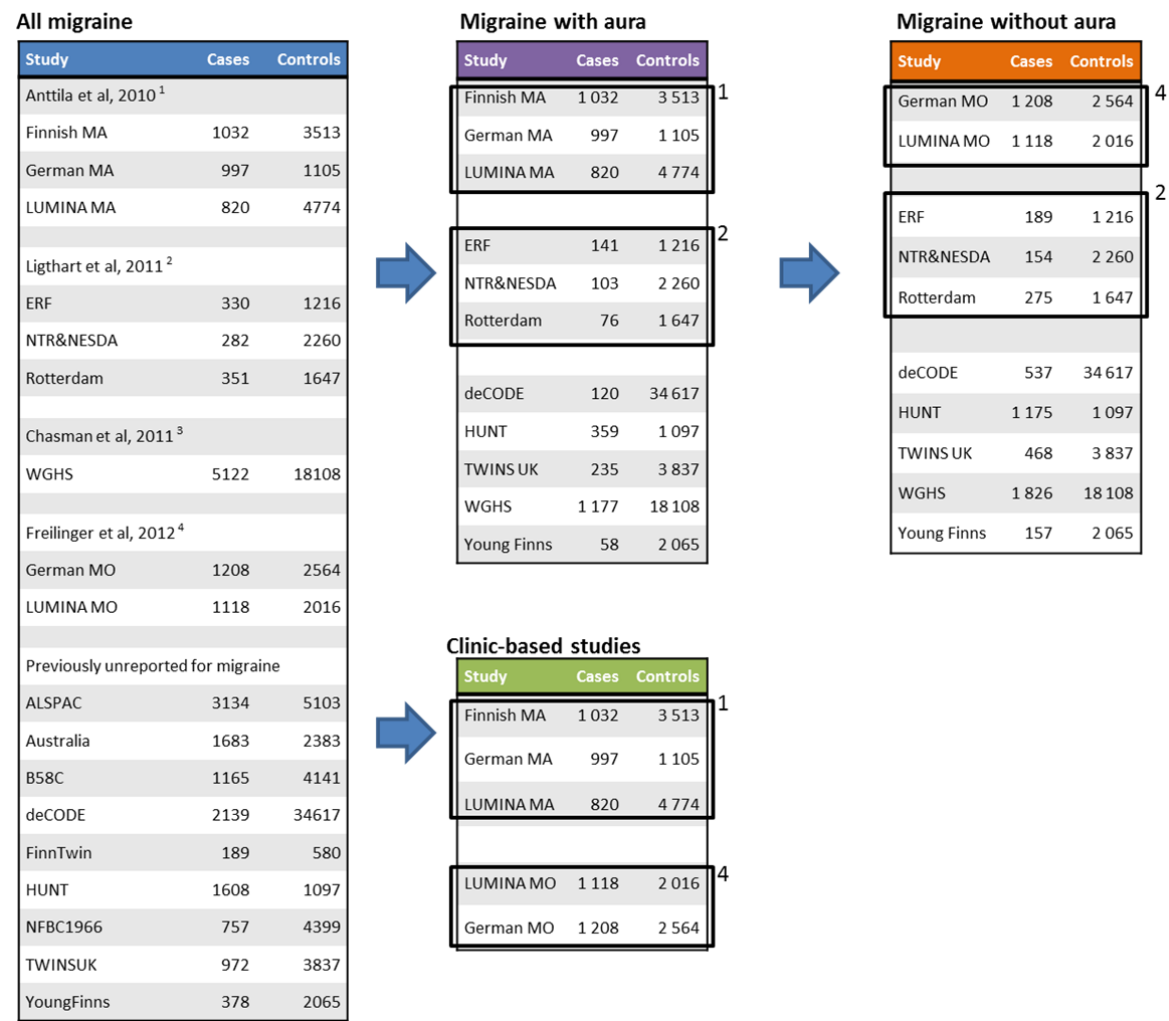
Supplementary Figures

Supplementary Figure 1. Participating studies



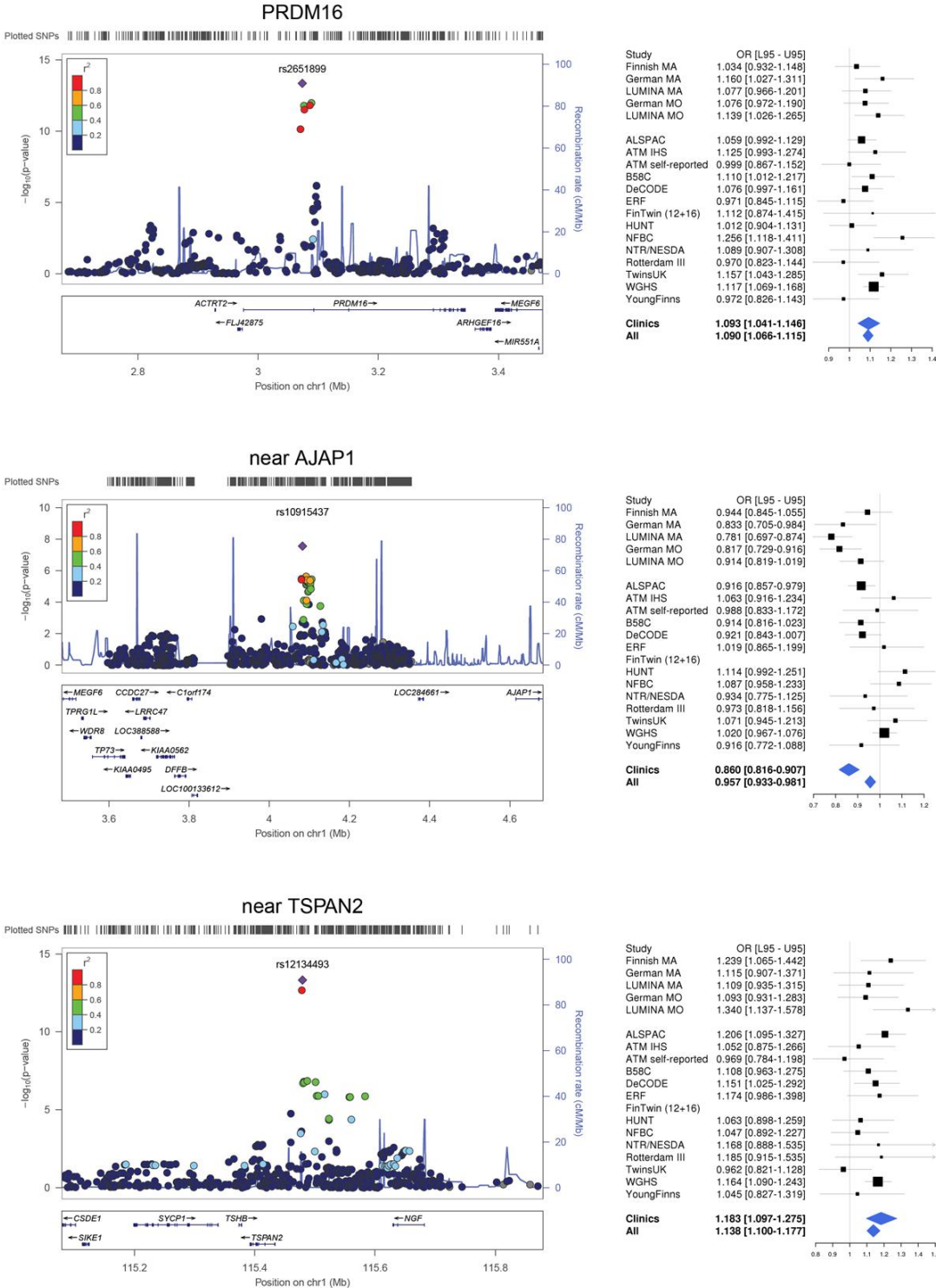
Please see section 'Participating Cohorts' for further information.

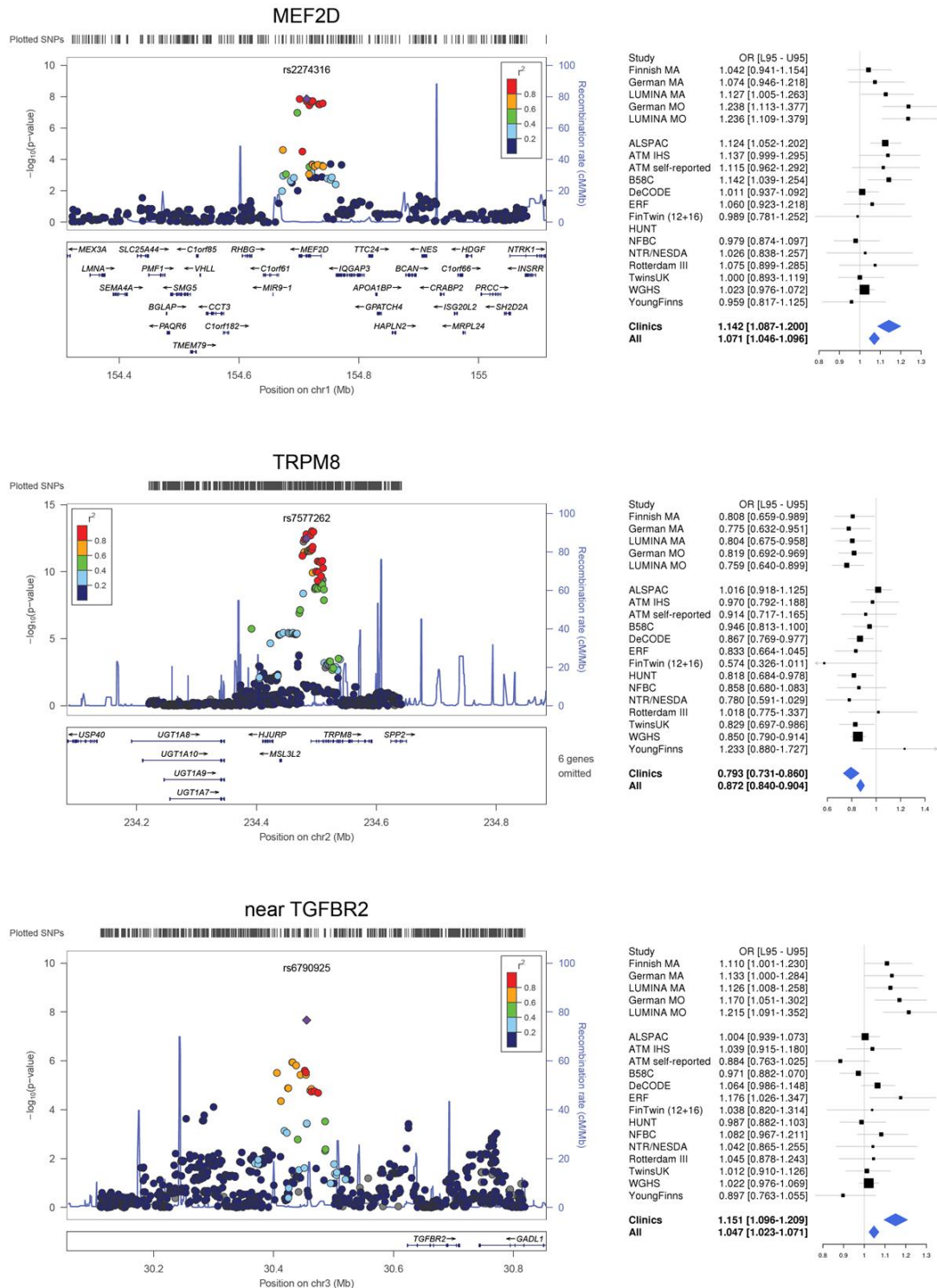
Supplementary Figure 2. Previously published study sets within the meta-analysis



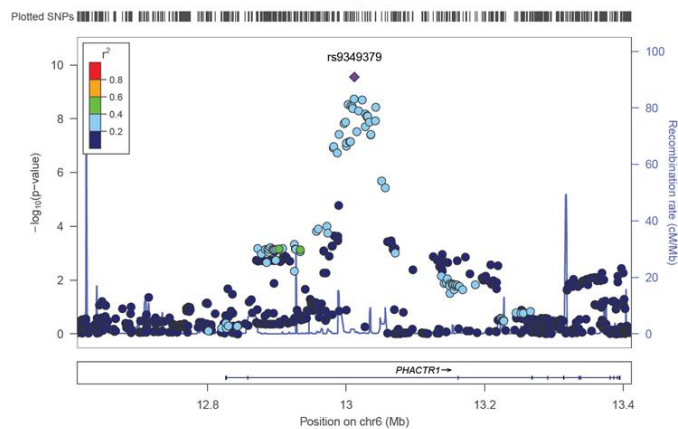
The boxes highlight the phenotypic subgroups used in the analysis and their sizes, with black outlines within them denoting which studies have been analysed together in previous publications. The numbers next to the black outlines show the original publications¹⁻⁴.

Supplementary Figure 3. Association plots of the identified significant loci

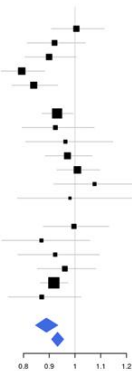




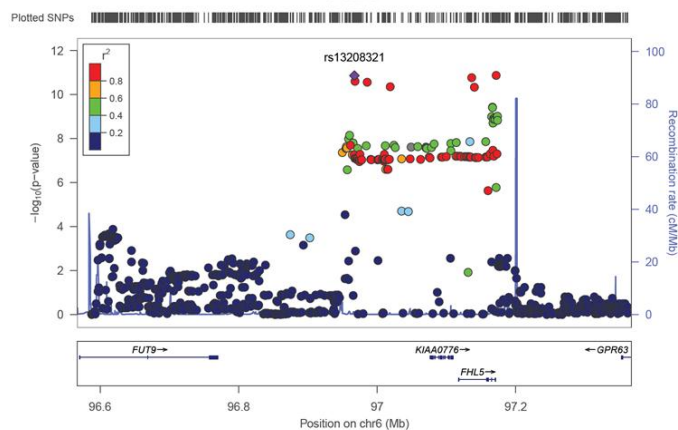
PHACTR1



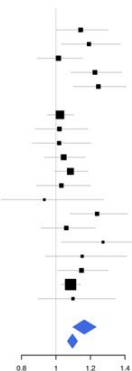
| Study | OR [L95 - U95] |
|-------------------|----------------------------|
| Finnish MA | 1.005 [0.908-1.113] |
| German MA | 0.921 [0.814-1.041] |
| LUMINA MA | 0.899 [0.805-1.005] |
| German MO | 0.793 [0.713-0.882] |
| LUMINA MO | 0.840 [0.755-0.934] |
| ALSPAC | 0.931 [0.872-0.993] |
| ATM IHS | 0.924 [0.794-1.075] |
| ATM self-reported | 0.963 [0.808-1.147] |
| B58C | 0.971 [0.884-1.066] |
| DeCODE | 1.010 [0.930-1.096] |
| ERF | 1.076 [0.918-1.261] |
| FinTwin (12+16) | 0.981 [0.777-1.237] |
| HUNT | |
| NFBC | 0.996 [0.877-1.132] |
| NTR/NESDA | 0.870 [0.715-1.057] |
| Rotterdam III | 0.923 [0.778-1.095] |
| TwinsUK | 0.961 [0.854-1.081] |
| WGHS | 0.918 [0.866-0.973] |
| YoungFinns | 0.871 [0.741-1.023] |
| Clinics | 0.889 [0.847-0.933] |
| All | 0.932 [0.909-0.956] |



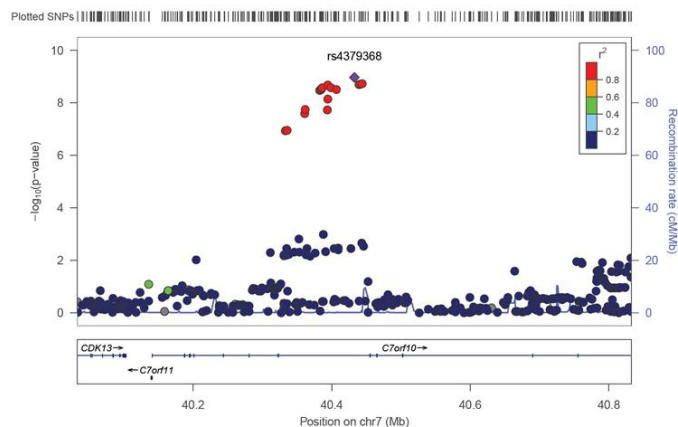
FHL5



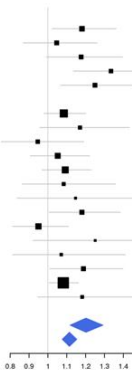
| Study | OR [L95 - U95] |
|-------------------|----------------------------|
| Finnish MA | 1.143 [1.003-1.303] |
| German MA | 1.191 [1.035-1.375] |
| LUMINA MA | 1.014 [0.892-1.154] |
| German MO | 1.226 [1.088-1.381] |
| LUMINA MO | 1.246 [1.102-1.408] |
| ALSPAC | 1.023 [0.950-1.102] |
| ATM IHS | 1.020 [0.879-1.184] |
| ATM self-reported | 1.019 [0.863-1.202] |
| B58C | 1.045 [0.934-1.169] |
| DeCODE | 1.084 [0.992-1.185] |
| ERF | 1.031 [0.887-1.199] |
| FinTwin (12+16) | 0.933 [0.683-1.274] |
| HUNT | 1.238 [1.083-1.417] |
| NFBC | 1.060 [0.914-1.229] |
| NTR/NESDA | 1.273 [1.032-1.571] |
| Rotterdam III | 1.152 [0.941-1.410] |
| TwinsUK | 1.148 [1.011-1.304] |
| WGHS | 1.085 [1.030-1.142] |
| YoungFinns | 1.099 [0.898-1.344] |
| Clinics | 1.164 [1.099-1.232] |
| All | 1.096 [1.067-1.125] |

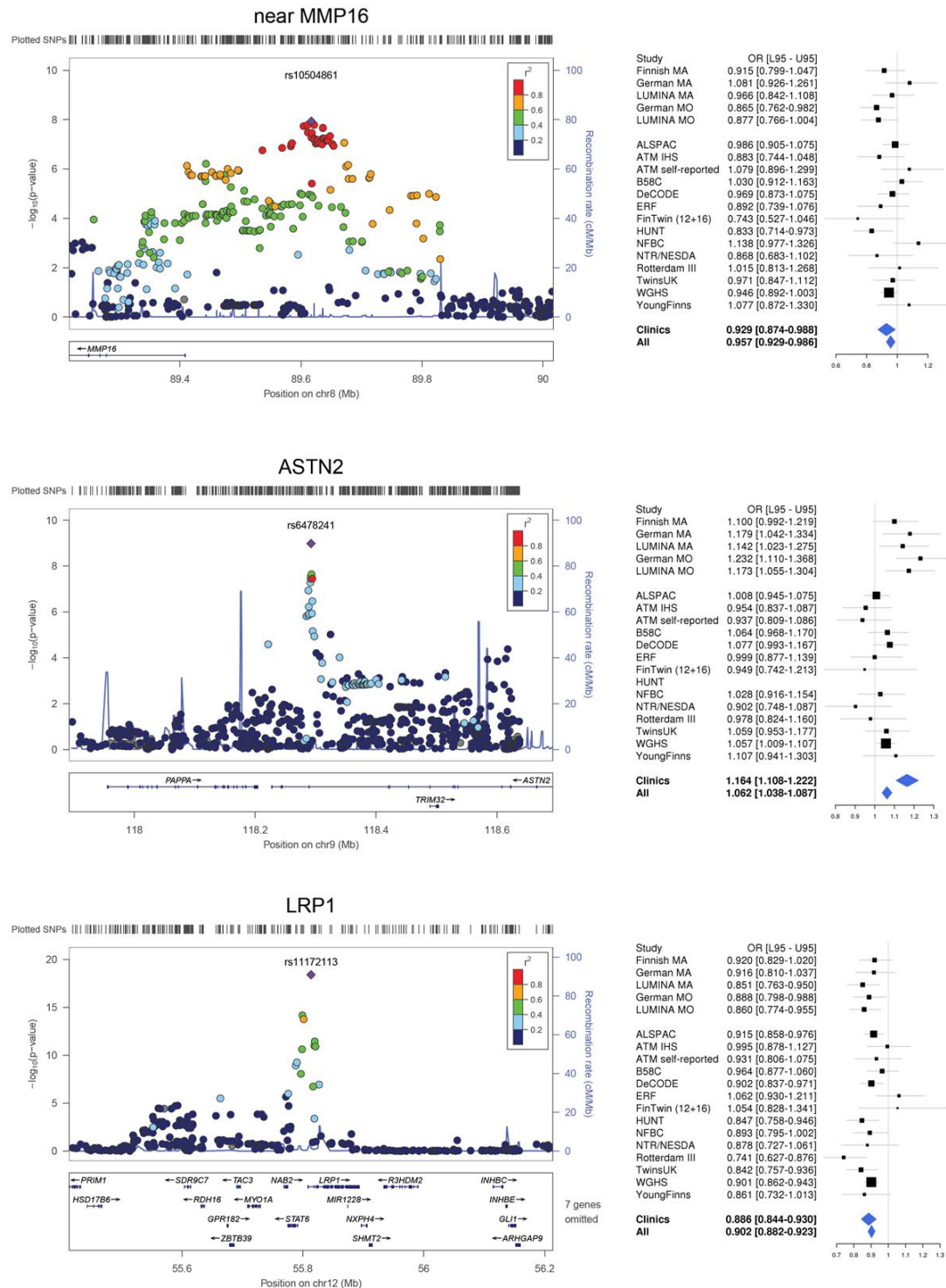


c7orf10



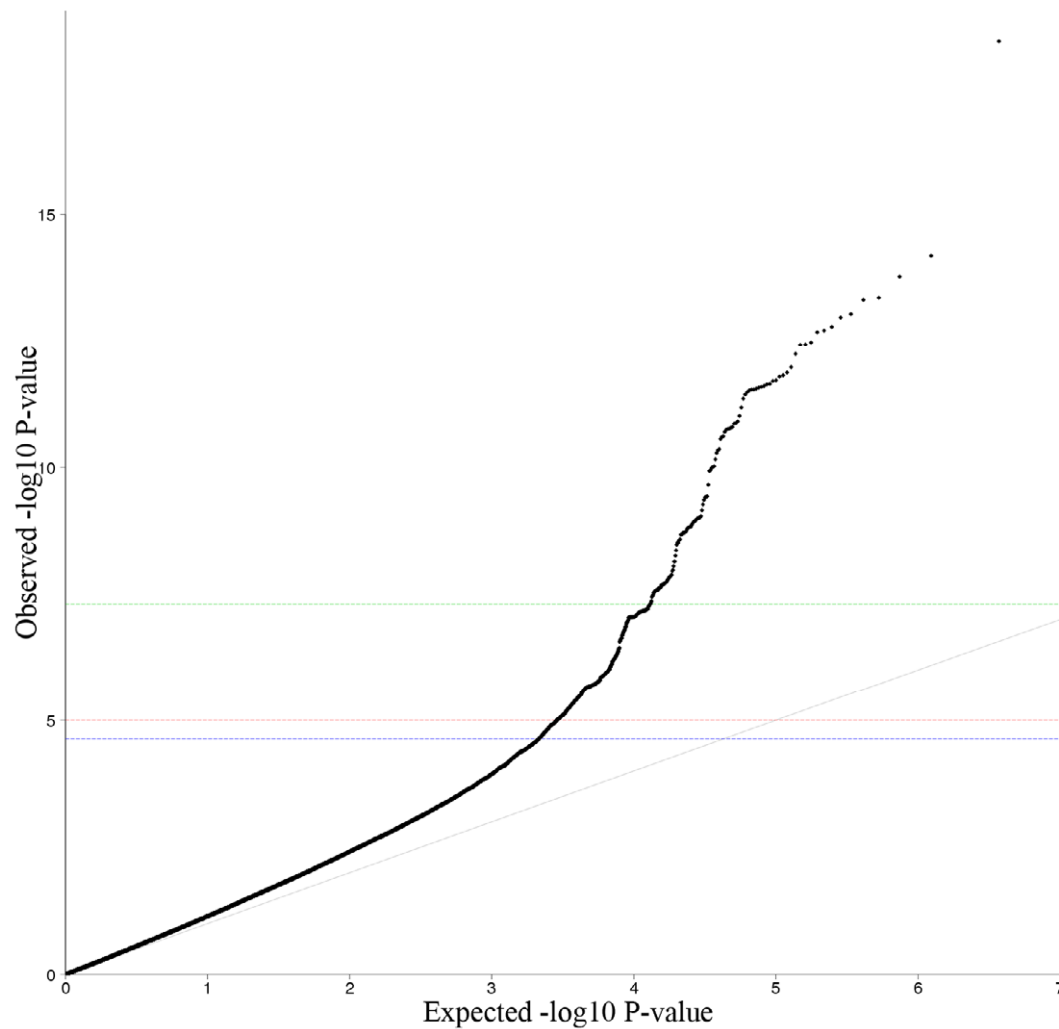
| Study | OR [L95 - U95] |
|-------------------|----------------------------|
| Finnish MA | 1.181 [1.023-1.363] |
| German MA | 1.047 [0.869-1.261] |
| LUMINA MA | 1.176 [0.991-1.396] |
| German MO | 1.334 [1.135-1.568] |
| LUMINA MO | 1.250 [1.066-1.464] |
| ALSPAC | 1.084 [0.979-1.201] |
| ATM IHS | 1.170 [0.957-1.431] |
| ATM self-reported | 0.946 [0.752-1.190] |
| B58C | 1.052 [0.907-1.221] |
| DeCODE | 1.092 [0.969-1.230] |
| ERF | 1.084 [0.865-1.358] |
| FinTwin (12+16) | 1.146 [0.837-1.571] |
| HUNT | 1.180 [1.007-1.384] |
| NFBC | 0.950 [0.813-1.109] |
| NTR/NESDA | 1.251 [0.922-1.696] |
| Rotterdam III | 1.071 [0.813-1.410] |
| TwinsUK | 1.188 [1.010-1.398] |
| WGHS | 1.082 [1.007-1.162] |
| YoungFinns | 1.182 [0.946-1.476] |
| Clinics | 1.202 [1.117-1.292] |
| All | 1.114 [1.076-1.153] |





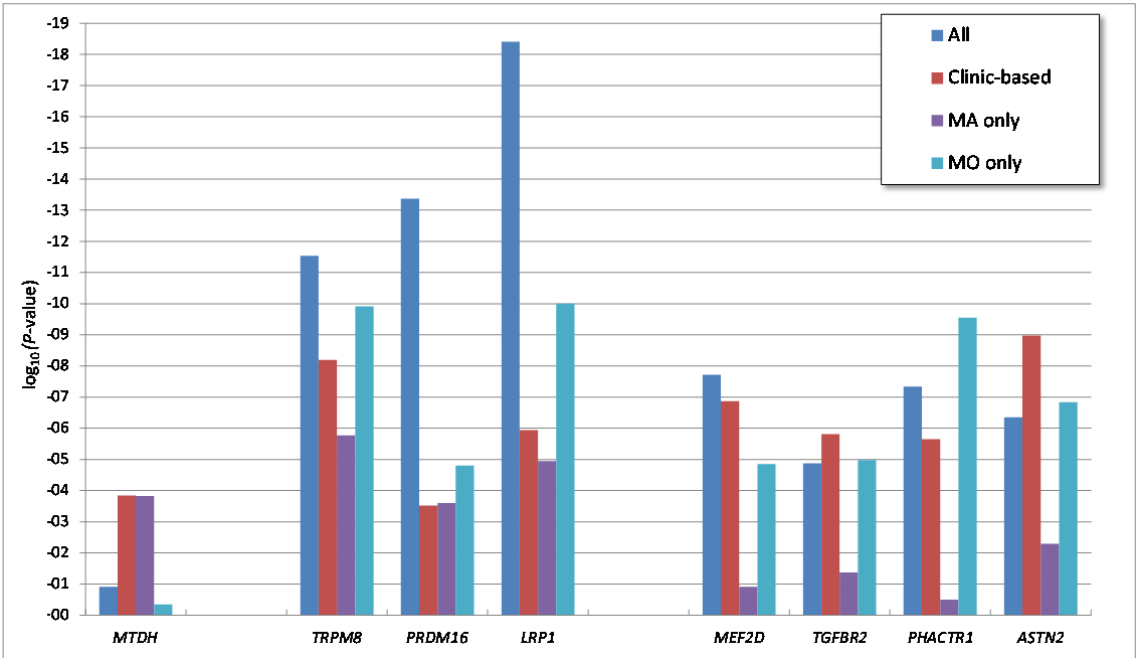
Plots showing the P values for association to migraine as well as the local recombination rate (left), together with forest plots showing the odds ratios for migraine in participating studies (clinic-based studies first, followed by the population cohorts) and the meta-analysis for clinic-based samples and all samples (right). Recombination rate data from 1000 Genomes June 2010 release for CEU. Positions are given as in build 36/hg18. The extent of LD to the SNP named in the plot is shown in the shading.

Supplementary Figure 4. Quantile-quantile plot of the meta-analysis results.



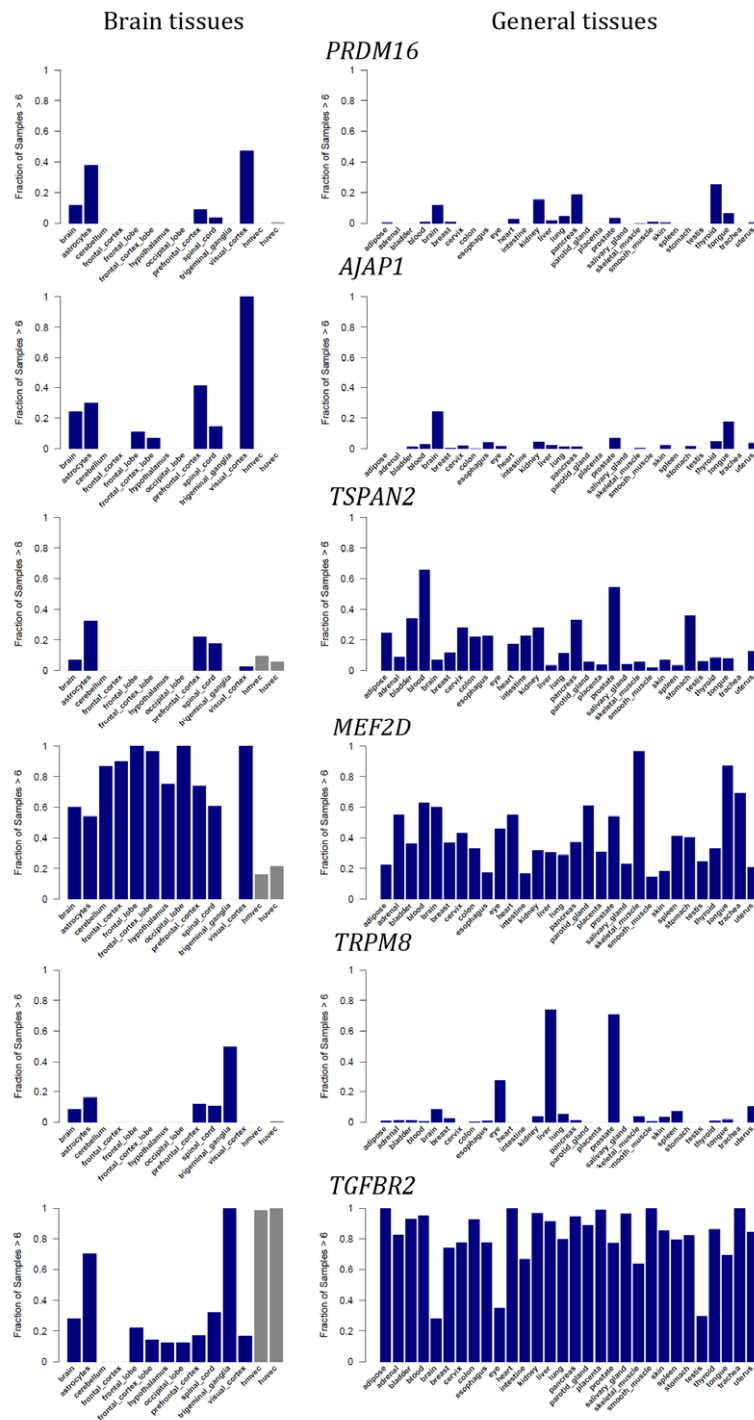
The dashed lines indicate thresholds for genome-wide significance (green; $P 5.0 \times 10^{-8}$), suggestive associations (red; $P 1 \times 10^{-5}$), and the false discovery rate <0.05 threshold (blue; $P 2.33 \times 10^{-5}$).

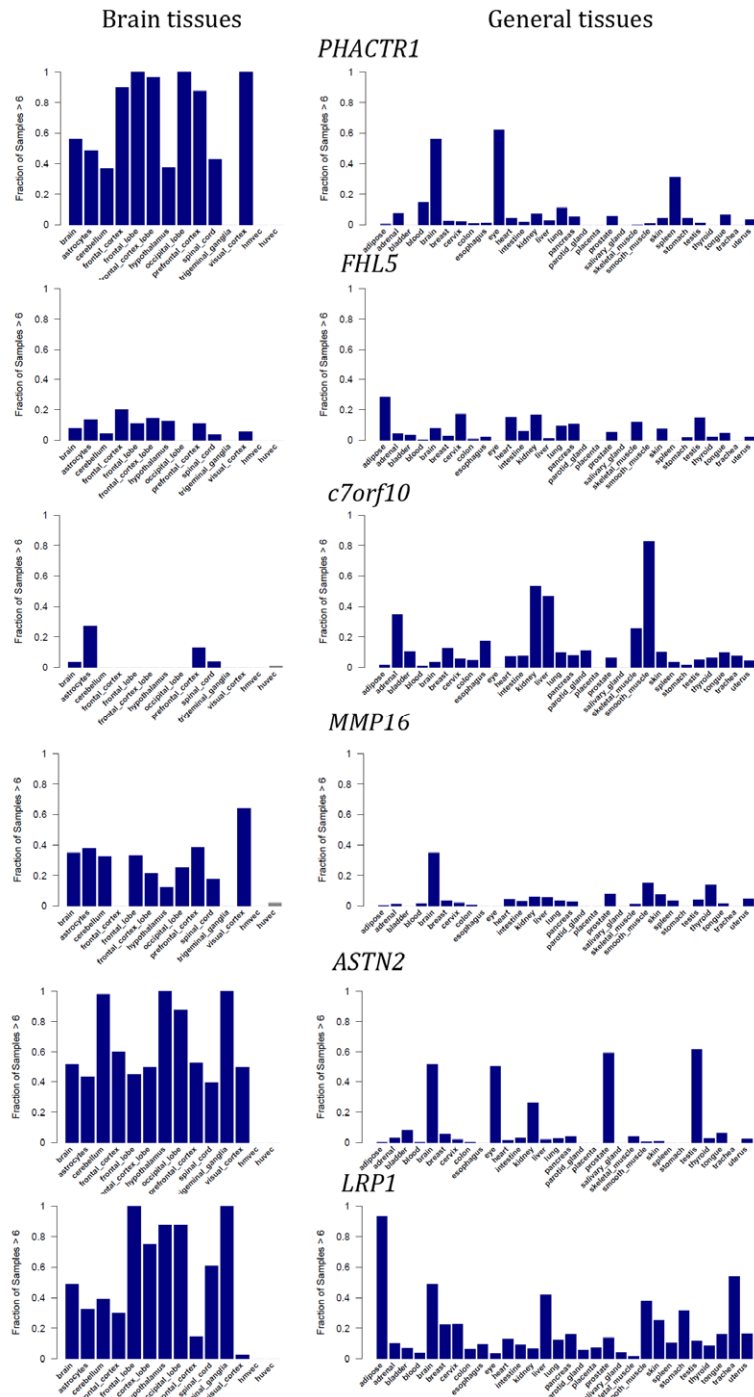
Supplementary Figure 5. Meta-analysis association results at previously reported migraine loci.



Plot showing the P values of the previously reported migraine-associated SNPs (see text for references) in order of publication in the meta-analyses of all samples and the three subsets.

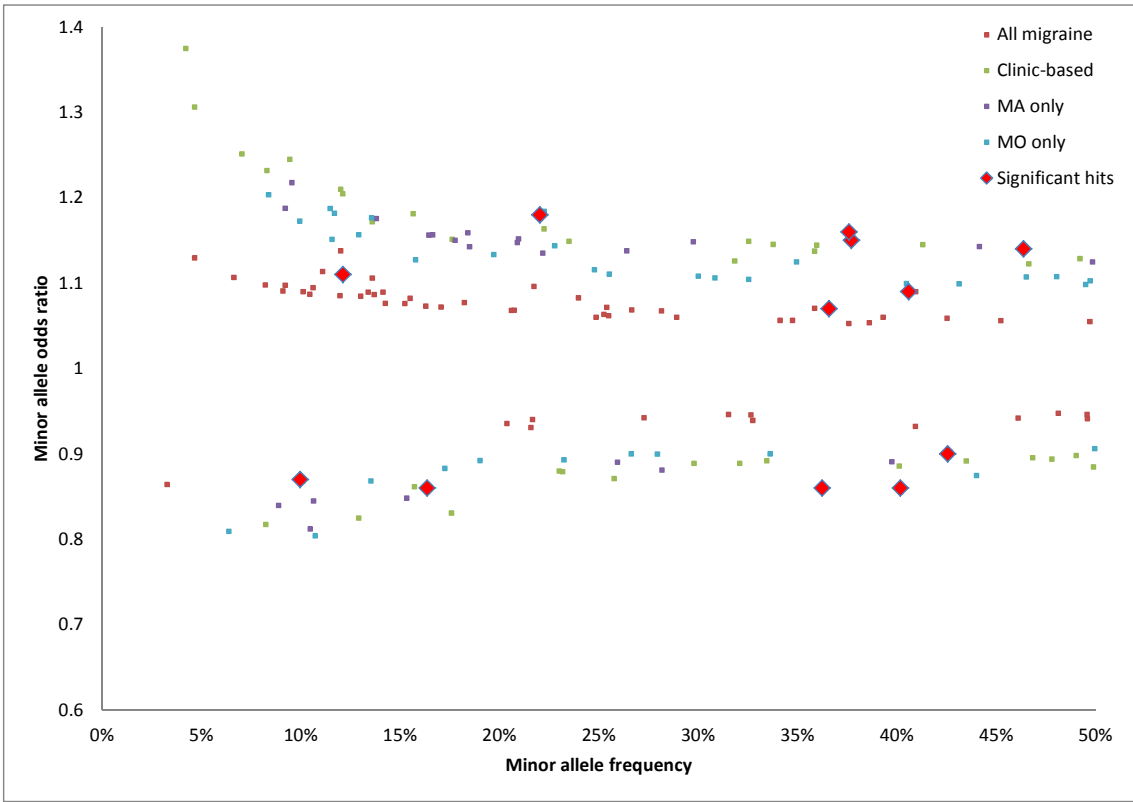
Supplementary Figure 6. Expression of genes with significant association to migraine reported in this study across 55,269 tissue samples





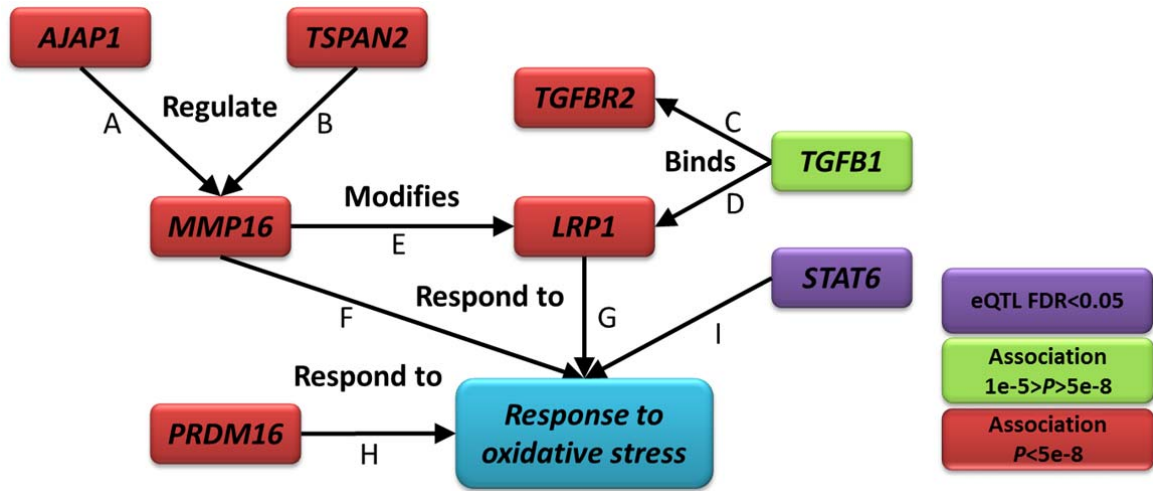
Number of samples for each tissue. Left panel: brain – 1,990; astrocytes – 37; cerebellum – 46; frontal cortex – 10; frontal lobe – 18; frontal cortex/lobe – 28; hypothalamus - 16; occipital lobe – 16; pre-frontal cortex 153; spinal cord – 28; trigeminal ganglia 16; visual cortex – 36; HMVEC (Human Microvascular Endothelial Cells) - 74, HUVEC (Human Umbilical Vein Endothelial Cells) - 310. The left panel contains, in addition to brain tissues, two sets of endothelial tissues (HMVEC and HUVEC). Right panel: adipose – 394; adrenal – 69; bladder – 86; blood – 3327; brain – 1990; breast – 4104; cervix – 53; colon – 1466; esophagus – 97; eye – 63; heart – 178; intestine – 66; kidney – 675; liver – 721; lung – 1442; pancreas – 150; parotid gland – 18; placenta – 107; prostate – 578; salivary gland – 26; skeletal muscle – 793; smooth muscle – 151; skin – 947; spleen – 29; stomach – 67; testis – 102; thyroid – 108; tongue – 62; trachea – 13; uterus – 212.

Supplementary Figure 7. Distribution of minor allele odds ratios (at loci with P value $< 1 \times 10^{-5}$) versus allele frequency



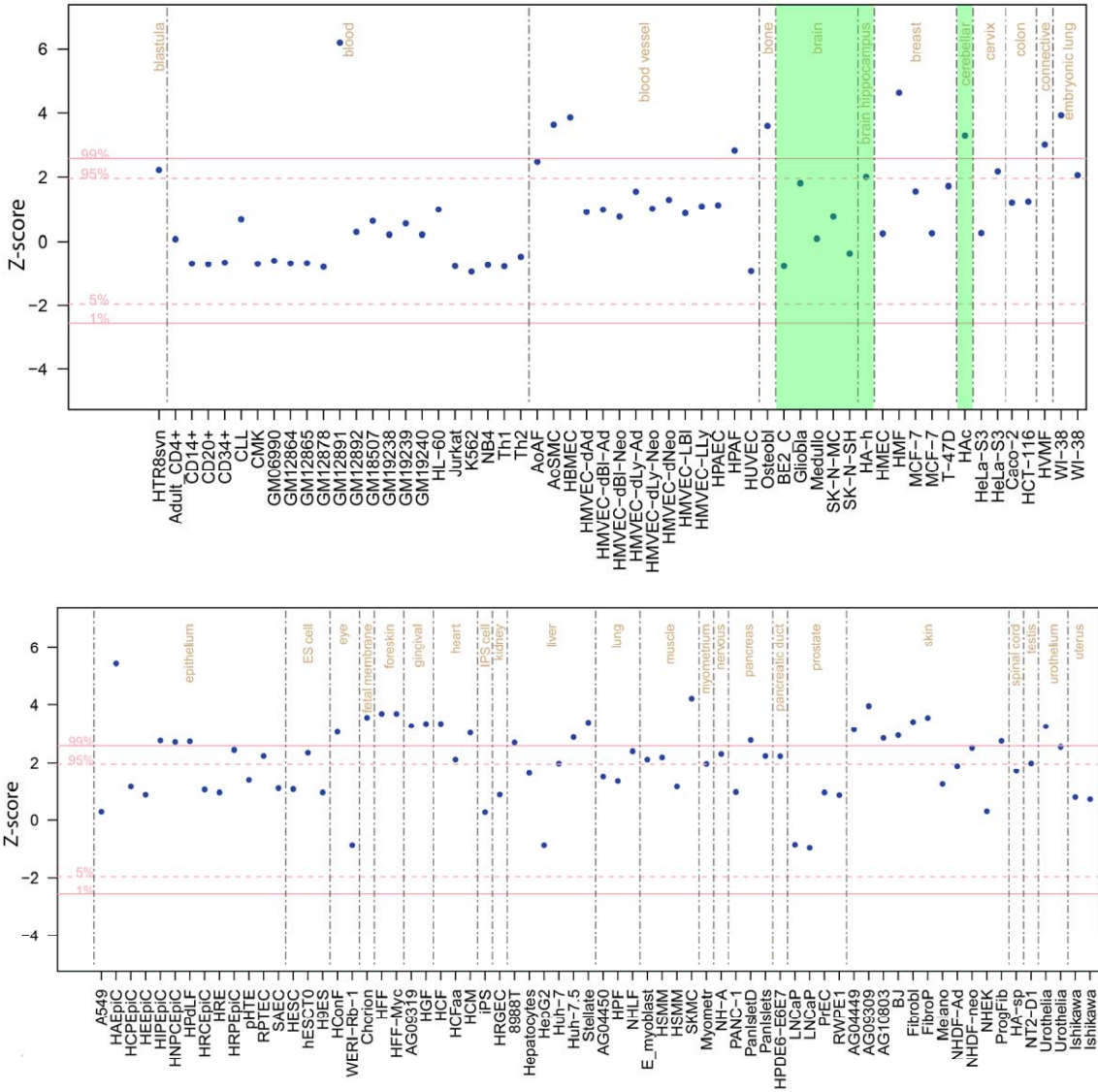
Plot comparing the frequency and odds ratios for the minor alleles reported in this study (suggestive and significant loci), showing an excess of risk increasing variants, especially towards lower frequencies.

Supplementary Figure 8. Hypothesis of how direct connections between genes at loci with significant association to migraine could potentially contribute to responses to oxidative stress.



Genes in red boxes are significantly associated with migraine. References – A^{5,6} (via CD147), B⁷, C⁸, D⁹, E¹⁰, F¹¹, G¹², H¹³, I¹⁴.

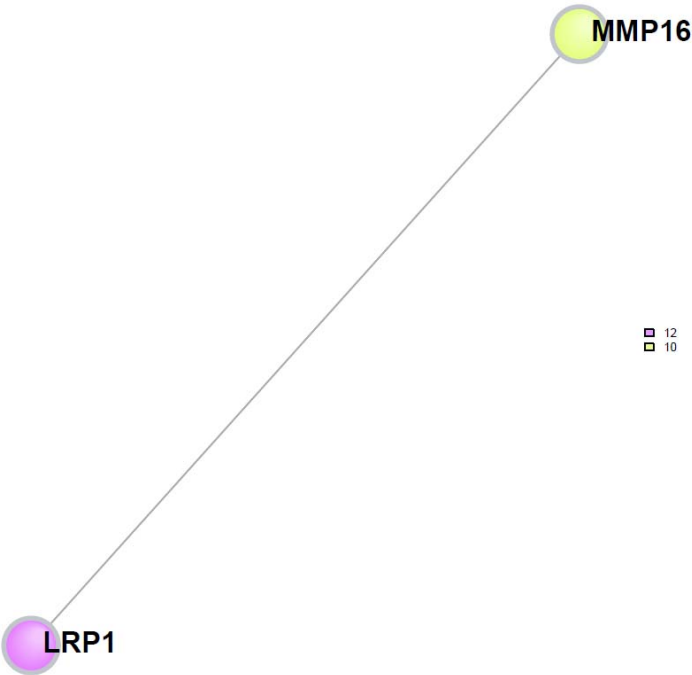
Supplementary Figure 9. DNase I hypersensitivity site abundance in ENCODE tissue data at migraine loci



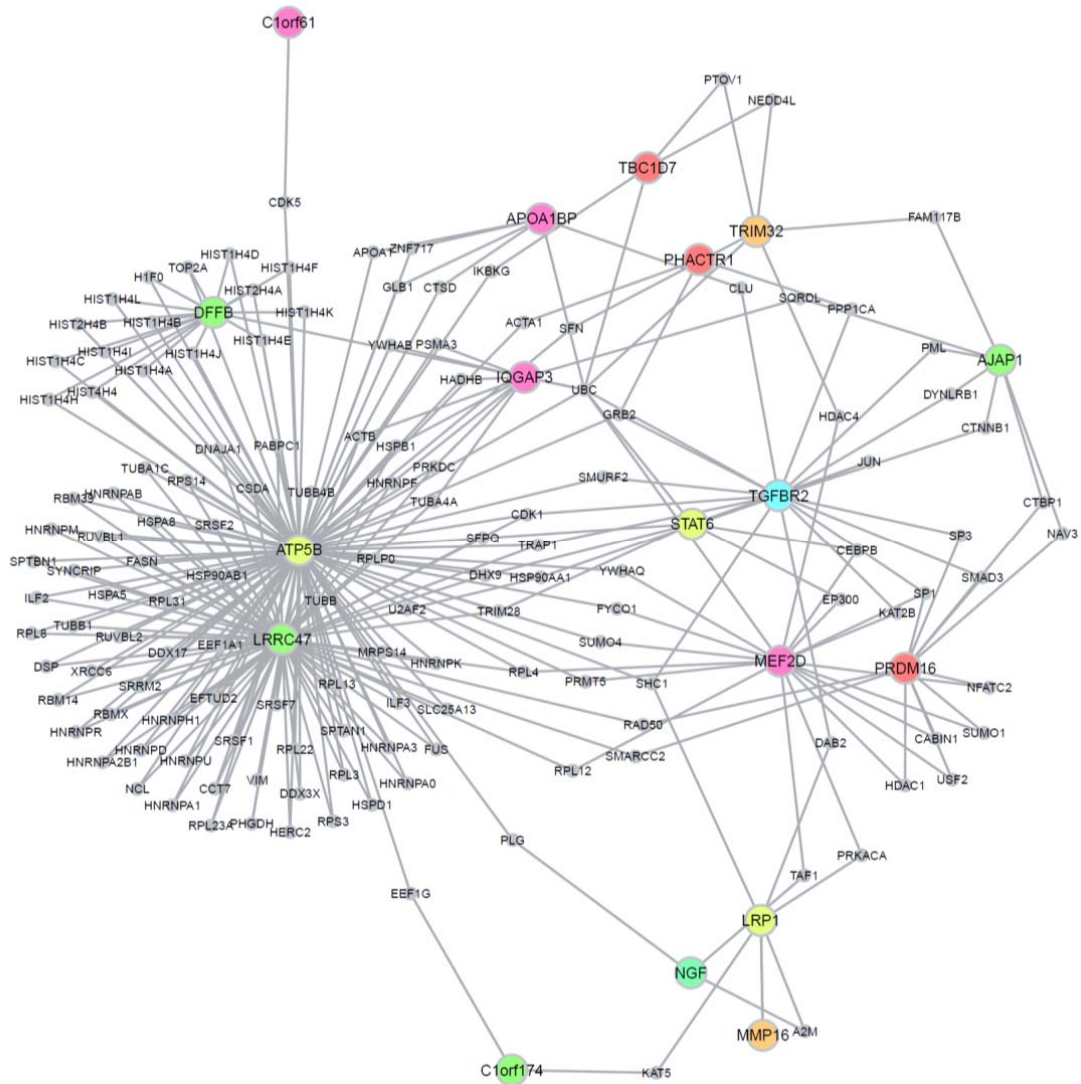
Plots showing the extremity of the proportion of loci containing DNase I hypersensitivity sites in each tissue for loci with significant association to migraine (P -value $< 5 \times 10^{-8}$). The dots indicate z scores for each cell line as defined by the mean and a variance of a 100 matched sets of SNPs (see Online Methods). Brain tissues are highlighted in green. The brown text at the top lists the tissue category, while the X-axis lists the exact tissue sample name (for further information, see <http://encodeproject.org/ENCODE/dataMatrix/encodeDataMatrixHuman.html>).

Supplementary Figure 10. Direct protein-protein interactions identified in the DAPPLE analysis

A)



B)



Plot of results from the DAPPLE analysis showing A) direct connections between the significant migraine loci and B) the whole network among significant loci. The colors reflect the different loci used as seeds for the analysis.

Supplementary Tables

Supplementary Table 1: Description of cases and controls from the clinical studies

| Study | Cases/ Controls | Migraine % | Female % of | | Ethnicity | Migraine definition | Control definition* | Ref study PMID |
|-----------------------------|--------------------|---------------|-------------|----------|-------------------------------|------------------------|------------------------|-----------------------|
| | | | Cases | Controls | | | | |
| German MO | 1208/2564 | 32.0 | 87.0 | 55.1 | | | | |
| MO cases | 1208/0 | | | | European, German | ICHD-II | | 22683712 |
| GSK | 0/861 | | | | | | Pop. | 19107115 |
| KORA | 0/834 | | | | | | Pop. | 16032514 |
| MPIPSYKL | 0/489 | | | | | | Pop. | - |
| HNR | 0/380 | | | | | | Pop. | 12177636 |
| LUMINA MO | 1118/2016 | 35.7 | 85.8 | 54.2 | | | | |
| MO cases | 1118/0 | | | | European, Dutch | ICHD-II | | 21914734; 22683712 |
| Rotterdam II | 0/2016 | | | | | | Pop. | 21877163 |
| Finnish MA | 1032/3513 | 22.7 | 80.2 | 52.6 | | | | |
| MA cases | 1032/0 | | | | European, Finnish | ICHD-II | | 11509082; 20802479 |
| Health 2000 | 0/1862 | | | | | | Mig-free | 20532202 |
| Helsinki Birth Cohort Study | 0/1651 | | | | | | Pop. | 16251536 |
| German MA study | 997/1105 | 47.4 | 81.1 | 60.8 | | | | |
| MA cases | 997/0 | | | | European, German | ICHD-II | | 20802479 |
| PopGen | 0/661 | | | | | | Pop. | 16490960 |
| Illumina iControlDB | 0/444 | | | | MDS- filtered Caucasian | | Pop. | |
| LUMINA MA | 820/4774 | 14.7 | 82.2 | 58.6 | | | | |
| MA cases | 820/0 | | | | European, Dutch | ICHD-II | | 21914734; 20802479 |
| Rotterdam I | 0/4774 | | | | | | Pop. | 21877163 |

Where more than one control definition was used, control groups are listed in decreasing size. The indented rows describe studies that were combined together to generate the set named on the first line of the set.

ICHD-II – cases fulfil the International Classification of Headache Disorders, 2nd edition definition for current or past migraine¹⁵. Pop. – Unscreened population-matched population-based sample. Mig-free pop. – migraine-free population-matched population-based sample. PMID – PubMed ID. MA – migraine with aura. MO – migraine without aura

Supplementary Table 2: Description of cases and controls from the population-based studies

| Study | Cases/ Controls | Migraine % | Female % of | | Ethnicity | Migraine definition | Control definition* | Ref study PMID |
|------------------|--------------------|---------------|-------------|----------|------------------------|--|---|-------------------------------------|
| | | | Cases | Controls | | | | |
| ALSPAC | 3134/ 5103 | 38.0 | 100 | 100 | European, British | Self-reported migraine, current or prior | No migraine or use of migraine medications; pop. | 22507742 |
| Australia ATM | 1683/ 2383 | 41.4 | 72.3 | 48.6 | European descent | Modified ICHD-II criteria, current migraine | Pop. | 20303062, 18676988 |
| B58C | 1165/ 4141 | 22.0 | 68.4 | 44.7 | European, British | Self-reported migraine, current or prior | No migraine or severe recurrent headaches | 16155052 |
| deCode | 2139/ 34617 | 5.8 | 73.8 | 55.4 | European, Icelandic | Full ICHD-II criteria, current migraine | Pop.; no migraine | 17038039 |
| ERF | 330/ 1216 | 21.3 | 75.5 | 50.6 | European, Dutch | Full ICHD-II criteria, current migraine | No migraine | 20071666 |
| FinnTwin | 189/ 580 | 28.5 | 63.5 | 46 | European, Finnish | Self-reported migraine, current or prior | No migraine, use of migraine medication or severe recurrent headaches | 12537859 , 12537860, 20953688 |
| HUNT | 1608/ 1097 | 59.4 | 74.9 | 75 | European, Norwegian | Self-reported migraine or fulfilling Modified ICHD-II criteria, current migraine | No migraine; pop. | 10999674 |
| NTR | 265/ 2128 | 11.1 | 85.3 | 55.2 | European, Dutch | Modified ICHD-II criteria, current migraine | No migraine or severe recurrent headache | 17254420, 16611468 |
| NESDA | 17/ 132 | 11.4 | 82.4 | 56.1 | European, Dutch | Modified ICHD-II criteria, current migraine | No migraine or severe recurrent headache | 18763692, 20713558 |
| NFBC1966 | 757/ 4399 | 14.7 | 76.5 | 48.2 | European, Finnish | Self-reported migraine, current or prior | No migraine | 4911003 |
| Rotterdam III | 351/ 1647 | 17.6 | 77.5 | 51.2 | European, Dutch | Modified ICHD-II criteria, current migraine | No migraine | 21877163 |
| Twins UK | 972/ 3837 | 20.2 | 96.2 | 89.8 | European, British | Self-reported migraine or fulfilling Modified ICHD-II criteria, current or prior migraine | No migraine | 22253318 |
| WGHS | 5122/ 18108 | 22.0 | 100 | 100 | European descent | Self-reported migraine or fulfilling Modified ICHD-II criteria, current | No migraine | 16849661, 18070814 |
| Young Finns | 378/ 2065 | 15.5 | 79.6 | 49.3 | European, Finnish | Full ICHD-II criteria, current migraine | No migraine | 18263651 |
| WGHS | 5122/ 18108 | 22.0 | 100 | 100 | European descent | Self-reported migraine or fulfilling Modified ICHD-II criteria, current or prior migraine | No migraine | 16849661, 18070814 |

Where more than one control definition was used, control groups are listed in decreasing size.

Pop. – Unscreened population-matched control sample. ICHD-II – International Classification of Headache Disorders, 2nd edition¹⁵.

Supplementary Table 3. Number of samples by phenotypes in study cohorts

| | ALSPAC | | ATM | | B58C | | DeCODE | | ERF | | FinnTwin | | HUNT | |
|---|--------|----------|-------|----------|-------|----------|--------|----------|-------|----------|----------|----------|-------|----------|
| | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls |
| Final number of samples for analysis | 3134 | 5103 | 1683 | 2383 | 1165 | 4141 | 2139 | 34617 | 330 | 1216 | 189 | 580 | 1608 | 1097 |
| Women | 3134 | 5103 | 1217 | 1158 | 797 | 1851 | 1711 | 19169 | 249 | 615 | 120 | 267 | 1204 | 823 |
| Men | 0 | 0 | 466 | 1225 | 368 | 2290 | 428 | 15448 | 81 | 601 | 69 | 313 | 404 | 274 |
| Samples fulfilling IHS migraine criteria | 0 | 0 | 886 | 1586 | 0 | 0 | 1352 | 34617 | 330 | 1216 | 0 | 0 | 1534 | 1097 |
| Women | 0 | 0 | 732 | 763 | 0 | 0 | 1069 | 19169 | 249 | 615 | 0 | 0 | 1140 | 823 |
| Men | 0 | 0 | 154 | 823 | 0 | 0 | 283 | 15448 | 81 | 601 | 0 | 0 | 394 | 274 |
| Self-reported migraine | 3134 | 5103 | 797 | 797 | 1165 | 4141 | 787 | 34617 | 0 | 0 | 189 | 580 | 74 | NA |
| Women | 3134 | 5103 | 485 | 395 | 797 | 1851 | 642 | 19169 | 0 | 0 | 120 | 267 | 64 | NA |
| Men | 0 | 0 | 312 | 402 | 368 | 2290 | 145 | 15448 | 0 | 0 | 69 | 313 | 10 | NA |
| Samples with migraine with aura | 0 | 0 | 0 | 0 | 0 | 0 | 120 | 34617 | 141 | 1216 | 0 | 0 | 359 | 1097 |
| Samples with migraine without aura analysis | 0 | 0 | 0 | 0 | 0 | 0 | 537 | 34617 | 189 | 1216 | 0 | 0 | 1175 | 1097 |

| | NTR | | NESDA | | NFBC1966 | | Rotterdam III | | TwinsUK | | WGHS | | YoungFinns | |
|---|-------|----------|-------|----------|----------|----------|---------------|----------|---------|----------|-------|----------|------------|----------|
| | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls |
| Final number of samples for analysis | 265 | 2128 | 17 | 132 | 757 | 4399 | 351 | 1727 | 972 | 3837 | 5122 | 18108 | 378 | 2065 |
| Women | 226 | 1174 | 14 | 74 | 579 | 2120 | 272 | 844 | 935 | 3446 | 5122 | 18108 | 301 | 1019 |
| Men | 39 | 954 | 3 | 58 | 178 | 2279 | 79 | 803 | 37 | 391 | 0 | 0 | 77 | 1046 |
| Samples fulfilling IHS migraine criteria | 265 | 2128 | 17 | 132 | 0 | 0 | 351 | 1727 | 703 | 3837 | 3003 | 18108 | 215 | 2065 |
| Women | 226 | 1174 | 14 | 74 | 0 | 0 | 272 | 844 | 684 | 3443 | 3003 | 18108 | 184 | 1019 |
| Men | 39 | 954 | 3 | 58 | 0 | 0 | 79 | 803 | 19 | 394 | 0 | 0 | 31 | 1046 |
| Self-reported migraine | 0 | 0 | 0 | 0 | 757 | 4399 | 0 | 0 | 502 | 0 | 2119 | 0 | 0 | 0 |
| Women | 0 | 0 | 0 | 0 | 579 | 2120 | 0 | 0 | 478 | 0 | 2119 | 0 | 0 | 0 |
| Men | 0 | 0 | 0 | 0 | 178 | 2279 | 0 | 0 | 24 | 0 | 0 | 0 | 0 | 0 |
| Samples with migraine with aura | 98 | 2128 | 5 | 132 | 0 | 0 | 76 | 1647 | 235 | 3837 | 1177 | 18108 | 58 | 2065 |
| Samples with migraine without aura analysis | 142 | 2128 | 12 | 132 | 0 | 0 | 275 | 1647 | 468 | 3837 | 1826 | 18108 | 157 | 2065 |

| | Finnish MA | | German MA | | German MO | | LUMINA MA | | LUMINA MO | |
|---|------------|----------|-----------|----------|-----------|----------|-----------|----------|-----------|----------|
| | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls |
| Final number of samples for analysis | 1032 | 3513 | 997 | 1105 | 1208 | 2564 | 820 | 4774 | 1118 | 2016 |
| Women | 828 | 1849 | 809 | 672 | 1051 | 1412 | 674 | 2797 | 959 | 1092 |
| Men | 204 | 1664 | 188 | 433 | 157 | 1152 | 146 | 1977 | 159 | 924 |
| Samples fulfilling IHS migraine criteria | 1032 | 3513 | 997 | 1105 | 1208 | 2564 | 820 | 4774 | 1118 | 2016 |
| Women | 828 | 1849 | 809 | 672 | 1051 | 1412 | 674 | 2797 | 959 | 1092 |
| Men | 204 | 1664 | 188 | 433 | 157 | 1152 | 146 | 1977 | 159 | 924 |
| Self-reported migraine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Women | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Men | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Samples with migraine with aura | 1032 | 3513 | 997 | 1105 | 0 | 0 | 820 | 4774 | 0 | 0 |
| Samples with migraine without aura analysis | 0 | 0 | 0 | 0 | 1208 | 2564 | 0 | 0 | 1118 | 2016 |

MA – migraine with aura. MO – migraine without aura.

Supplementary Table 4. Association results at the loci with p-values less than 1×10^{-5}

| Marker | | | | Lowest p-value | | | | | All samples | | Clinics | | MA | | MO | | |
|------------|-----|-----------------------|--------------|-----------------|--------------------|---------|----------------|------|-------------|-----------------|--------------------|-----------------|--------------------|----------|--------------------|-----------------|--------------------|
| SNP | Chr | Position ^a | Minor allele | Lowest p-value | OR (95% CI) | Q-value | r ² | MAF | Group | P-value | OR | P-value | OR | P-value | OR | P-value | OR |
| rs2651899 | 1 | 3073572 | C | 4.34E-14 | 1.09 (1.07 - 1.11) | 0.23 | 0.18 | 0.41 | All | 4.34E-14 | 1.09 (1.07 - 1.11) | 3.06E-04 | 1.09 (1.04 - 1.15) | 2.54E-04 | 1.09 (1.04 - 1.14) | 1.56E-05 | 1.09 (1.05 - 1.14) |
| rs10737909 | 1 | 15421223 | G | 1.89E-07 | 0.94 (0.92 - 0.96) | 0.23 | 0.19 | 0.46 | All | 1.89E-07 | 0.94 (0.92 - 0.96) | 1.08E-02 | 0.94 (0.90 - 0.99) | 9.74E-03 | 0.94 (0.90 - 0.99) | 8.91E-05 | 0.92 (0.89 - 0.96) |
| rs1890566 | 1 | 54440866 | G | 7.97E-07 | 1.06 (1.04 - 1.08) | 0.22 | 0.19 | 0.43 | All | 7.97E-07 | 1.06 (1.04 - 1.08) | 1.23E-02 | 1.06 (1.01 - 1.12) | 1.52E-03 | 1.08 (1.03 - 1.13) | 9.74E-02 | 1.04 (0.99 - 1.08) |
| rs12134493 | 1 | 115479469 | A | 4.79E-14 | 1.14 (1.10 - 1.18) | 0.45 | 0.00 | 0.12 | All | 4.79E-14 | 1.14 (1.10 - 1.18) | 1.19E-05 | 1.18 (1.10 - 1.27) | 6.19E-04 | 1.13 (1.05 - 1.21) | 5.29E-08 | 1.18 (1.11 - 1.26) |
| rs2274316 | 1 | 154712866 | C | 1.42E-08 | 1.07 (1.05 - 1.10) | 0.02 | 0.47 | 0.36 | All | 1.42E-08 | 1.07 (1.05 - 1.10) | 1.43E-07 | 1.14 (1.09 - 1.20) | 8.66E-02 | 1.04 (0.99 - 1.10) | 2.31E-05 | 1.10 (1.05 - 1.15) |
| rs10442694 | 1 | 204800040 | T | 6.92E-05 | 0.95 (0.93 - 0.97) | 0.62 | 0.00 | 0.27 | All | 6.92E-05 | 0.95 (0.93 - 0.97) | 8.95E-01 | 1.00 (0.95 - 1.06) | 5.18E-02 | 0.95 (0.90 - 1.00) | 9.29E-01 | 1.00 (0.96 - 1.05) |
| rs6741751 | 2 | 234492400 | A | 9.11E-14 | 0.87 (0.84 - 0.90) | 0.10 | 0.31 | 0.10 | All | 9.11E-14 | 0.87 (0.84 - 0.90) | 1.09E-08 | 0.79 (0.73 - 0.86) | 1.03E-07 | 0.81 (0.75 - 0.88) | 8.64E-11 | 0.80 (0.75 - 0.86) |
| rs3923518 | 3 | 38861417 | A | 7.92E-06 | 1.06 (1.03 - 1.09) | 0.29 | 0.14 | 0.25 | All | 7.92E-06 | 1.06 (1.03 - 1.09) | 2.67E-02 | 1.06 (1.01 - 1.12) | 1.79E-02 | 1.06 (1.01 - 1.12) | 2.92E-02 | 1.05 (1.01 - 1.10) |
| rs10511112 | 3 | 80451153 | C | 4.71E-06 | 1.11 (1.06 - 1.16) | 0.68 | 0.00 | 0.07 | All | 4.71E-06 | 1.11 (1.06 - 1.16) | 5.82E-03 | 1.15 (1.04 - 1.26) | 2.83E-03 | 1.15 (1.05 - 1.26) | 1.24E-02 | 1.10 (1.02 - 1.19) |
| rs273218 | 5 | 53416312 | T | 2.34E-06 | 0.94 (0.91 - 0.96) | 0.19 | 0.21 | 0.20 | All | 2.34E-06 | 0.94 (0.91 - 0.96) | 1.07E-01 | 0.95 (0.90 - 1.01) | 1.07E-02 | 0.93 (0.88 - 0.98) | 1.05E-02 | 0.94 (0.89 - 0.98) |
| rs12519773 | 5 | 92490172 | C | 1.93E-06 | 0.95 (0.93 - 0.97) | 0.61 | 0.00 | 0.48 | All | 1.93E-06 | 0.95 (0.93 - 0.97) | 5.96E-03 | 0.93 (0.89 - 0.98) | 3.48E-03 | 0.93 (0.89 - 0.98) | 1.12E-02 | 0.95 (0.91 - 0.99) |
| rs2447820 | 5 | 122292635 | T | 4.15E-06 | 1.09 (1.05 - 1.13) | 0.64 | 0.00 | 0.10 | All | 4.15E-06 | 1.09 (1.05 - 1.13) | 7.10E-03 | 1.11 (1.03 - 1.19) | 7.20E-02 | 1.07 (0.99 - 1.15) | 3.80E-03 | 1.10 (1.03 - 1.18) |
| rs12153243 | 7 | 142879994 | T | 6.10E-06 | 1.05 (1.03 - 1.08) | 0.32 | 0.11 | 0.39 | All | 6.10E-06 | 1.05 (1.03 - 1.08) | 1.75E-04 | 1.10 (1.05 - 1.15) | 3.66E-04 | 1.09 (1.04 - 1.14) | 6.27E-03 | 1.06 (1.02 - 1.10) |
| rs11750092 | 5 | 159300549 | T | 6.51E-06 | 1.07 (1.04 - 1.11) | 0.67 | 0.00 | 0.16 | All | 6.51E-06 | 1.07 (1.04 - 1.11) | 1.23E-03 | 1.11 (1.04 - 1.19) | 3.11E-01 | 1.03 (0.97 - 1.10) | 2.79E-02 | 1.07 (1.01 - 1.13) |
| rs10456100 | 6 | 39291448 | T | 5.44E-07 | 1.07 (1.04 - 1.10) | 0.24 | 0.18 | 0.27 | All | 5.44E-07 | 1.07 (1.04 - 1.10) | 2.50E-05 | 1.13 (1.07 - 1.20) | 2.46E-01 | 1.03 (0.98 - 1.09) | 2.06E-04 | 1.09 (1.04 - 1.14) |
| rs543844 | 6 | 44532278 | G | 3.41E-06 | 1.06 (1.03 - 1.08) | 0.43 | 0.02 | 0.34 | All | 3.41E-06 | 1.06 (1.03 - 1.08) | 4.01E-02 | 1.05 (1.00 - 1.11) | 4.71E-02 | 1.05 (1.00 - 1.10) | 1.35E-04 | 1.08 (1.04 - 1.13) |
| rs13203080 | 6 | 136926504 | A | 5.33E-05 | 1.07 (1.03 - 1.10) | 0.32 | 0.11 | 0.15 | All | 5.33E-05 | 1.07 (1.03 - 1.10) | 9.05E-01 | 1.00 (0.94 - 1.07) | 9.69E-01 | 1.00 (0.94 - 1.06) | 7.32E-03 | 1.08 (1.02 - 1.14) |
| rs13196614 | 6 | 148965482 | T | 5.36E-06 | 1.08 (1.04 - 1.11) | 0.41 | 0.03 | 0.18 | All | 5.36E-06 | 1.08 (1.04 - 1.11) | 1.28E-02 | 1.10 (1.02 - 1.18) | 5.15E-02 | 1.07 (1.00 - 1.14) | 1.69E-02 | 1.07 (1.01 - 1.14) |
| rs13218732 | 6 | 153306903 | C | 3.44E-06 | 0.86 (0.81 - 0.92) | 0.68 | 0.00 | 0.03 | All | 3.44E-06 | 0.86 (0.81 - 0.92) | 2.24E-04 | 0.79 (0.70 - 0.89) | - | - | - | - |
| rs10244428 | 7 | 8488468 | T | 2.27E-05 | 0.95 (0.93 - 0.97) | 0.64 | 0.00 | 0.45 | All | 2.27E-05 | 0.95 (0.93 - 0.97) | 5.81E-01 | 0.99 (0.94 - 1.04) | 1.25E-02 | 1.06 (1.01 - 1.11) | 1.86E-02 | 0.95 (0.91 - 0.99) |
| rs4379368 | 7 | 40432725 | T | 1.07E-09 | 1.11 (1.08 - 1.15) | 0.44 | 0.01 | 0.11 | All | 1.07E-09 | 1.11 (1.08 - 1.15) | 7.18E-07 | 1.20 (1.12 - 1.29) | 1.24E-03 | 1.12 (1.05 - 1.20) | 5.81E-08 | 1.19 (1.12 - 1.27) |
| rs9649465 | 7 | 123163796 | A | 1.21E-06 | 1.06 (1.03 - 1.08) | 0.10 | 0.30 | 0.45 | All | 1.21E-06 | 1.06 (1.03 - 1.08) | 1.16E-02 | 1.06 (1.01 - 1.12) | 1.30E-03 | 1.08 (1.03 - 1.13) | 1.63E-02 | 1.05 (1.01 - 1.09) |
| rs1861960 | 7 | 154977896 | T | 6.30E-06 | 1.07 (1.04 - 1.10) | 0.08 | 0.34 | 0.20 | All | 6.30E-06 | 1.07 (1.04 - 1.10) | 8.11E-02 | 1.05 (0.99 - 1.12) | 2.27E-02 | 1.07 (1.01 - 1.13) | 3.10E-03 | 1.08 (1.03 - 1.14) |
| rs2946505 | 8 | 12855253 | T | 8.94E-06 | 0.94 (0.92 - 0.97) | 0.06 | 0.36 | 0.22 | All | 8.94E-06 | 0.94 (0.92 - 0.97) | 4.74E-01 | 0.98 (0.92 - 1.04) | 1.54E-02 | 0.93 (0.88 - 0.99) | 2.67E-01 | 0.97 (0.93 - 1.02) |
| rs12681963 | 8 | 30102060 | T | 2.05E-07 | 1.11 (1.06 - 1.15) | 1.00 | 0.00 | 0.14 | All | 2.05E-07 | 1.11 (1.06 - 1.15) | 5.54E-03 | 1.12 (1.03 - 1.20) | 1.81E-03 | 1.13 (1.05 - 1.22) | 2.56E-02 | 1.08 (1.01 - 1.16) |
| rs12681792 | 8 | 62217017 | A | 9.04E-07 | 0.93 (0.90 - 0.96) | 0.00 | 0.55 | 0.22 | All | 9.04E-07 | 0.93 (0.90 - 0.96) | 1.40E-01 | 0.95 (0.90 - 1.02) | 2.27E-02 | 0.93 (0.88 - 0.99) | 1.66E-04 | 0.90 (0.86 - 0.95) |
| rs13263568 | 8 | 72609972 | C | 1.84E-06 | 1.10 (1.06 - 1.14) | 0.71 | 0.00 | 0.09 | All | 1.84E-06 | 1.10 (1.06 - 1.14) | 1.25E-03 | 1.15 (1.06 - 1.26) | 9.50E-03 | 1.11 (1.03 - 1.21) | 6.57E-03 | 1.10 (1.03 - 1.18) |
| rs6998277 | 8 | 103709117 | G | 2.39E-06 | 1.07 (1.04 - 1.10) | 0.64 | 0.00 | 0.21 | All | 2.39E-06 | 1.07 (1.04 - 1.10) | 2.03E-02 | 1.07 (1.01 - 1.14) | 3.50E-03 | 1.09 (1.03 - 1.15) | 6.89E-03 | 1.07 (1.02 - 1.12) |
| rs4733750 | 8 | 131008307 | G | 2.01E-05 | 1.11 (1.06 - 1.16) | 0.30 | 0.13 | 0.06 | All | 2.01E-05 | 1.11 (1.06 - 1.16) | 5.32E-01 | 1.03 (0.93 - 1.14) | 2.22E-01 | 1.06 (0.97 - 1.16) | 7.77E-02 | 1.08 (0.99 - 1.17) |
| rs16904191 | 8 | 13102678 | T | 1.64E-07 | 1.07 (1.04 - 1.09) | 0.77 | 0.00 | 0.28 | All | 1.64E-07 | 1.07 (1.04 - 1.09) | 3.88E-01 | 1.02 (0.97 - 1.08) | 7.96E-02 | 1.05 (0.99 - 1.10) | 1.49E-02 | 1.06 (1.01 - 1.10) |
| rs12066166 | 9 | 117464808 | T | 8.51E-07 | 1.08 (1.05 - 1.12) | 0.93 | 0.00 | 0.16 | All | 8.51E-07 | 1.08 (1.05 - 1.12) | 3.82E-03 | 1.11 (1.03 - 1.19) | 1.45E-03 | 1.11 (1.04 - 1.19) | 1.51E-02 | 1.07 (1.01 - 1.14) |
| rs17303101 | 9 | 118221615 | A | 3.79E-07 | 1.07 (1.04 - 1.10) | 0.18 | 0.23 | 0.28 | All | 3.79E-07 | 1.07 (1.04 - 1.10) | 2.52E-05 | 1.13 (1.07 - 1.19) | 1.98E-02 | 1.06 (1.01 - 1.12) | 3.46E-04 | 1.09 (1.04 - 1.14) |
| rs7916968 | 10 | 749268 | G | 6.70E-06 | 1.09 (1.05 - 1.13) | 0.03 | 0.41 | 0.09 | All | 6.70E-06 | 1.09 (1.05 - 1.13) | 1.90E-01 | 1.05 (0.97 - 1.14) | 5.62E-03 | 1.11 (1.03 - 1.20) | 2.65E-02 | 1.08 (1.01 - 1.16) |
| rs4880487 | 10 | 1236883 | T | 3.33E-06 | 1.06 (1.04 - 1.09) | 0.00 | 0.72 | 0.25 | All | 3.33E-06 | 1.06 (1.04 - 1.09) | 9.57E-01 | 1.00 (0.95 - 1.05) | 4.64E-02 | 1.06 (1.00 - 1.11) | 1.93E-01 | 1.03 (0.98 - 1.08) |
| rs10904077 | 10 | 7310904 | G | 3.57E-05 | 1.10 (1.05 - 1.15) | 0.00 | 0.62 | 0.06 | All | 3.57E-05 | 1.10 (1.05 - 1.15) | 7.91E-01 | 1.01 (0.92 - 1.12) | 6.55E-03 | 1.13 (1.04 - 1.24) | - | - |
| rs11816922 | 10 | 6964450 | A | 5.37E-06 | 1.10 (1.05 - 1.14) | 0.01 | 0.47 | 0.08 | All | 5.37E-06 | 1.10 (1.05 - 1.14) | 1.91E-03 | 1.15 (1.05 - 1.25) | 2.06E-04 | 1.17 (1.08 - 1.27) | 7.87E-03 | 1.11 (1.03 - 1.20) |
| rs827382 | 10 | 8759275 | C | 9.11E-08 | 1.07 (1.04 - 1.10) | 0.00 | 0.68 | 0.25 | All | 9.11E-08 | 1.07 (1.04 - 1.10) | 9.64E-04 | 1.09 (1.04 - 1.16) | 4.76E-03 | 1.08 (1.02 - 1.13) | 1.26E-04 | 1.09 (1.04 - 1.14) |
| rs10906466 | 10 | 13830271 | A | 7.83E-06 | 1.06 (1.03 - 1.09) | 0.06 | 0.37 | 0.29 | All | 7.83E-06 | 1.06 (1.03 - 1.09) | 1.35E-01 | 1.04 (0.99 - 1.10) | 1.16E-03 | 1.09 (1.03 - 1.15) | - | - |
| rs11594111 | 10 | 14985412 | G | 1.37E-07 | 1.09 (1.06 - 1.12) | 0.02 | 0.45 | 0.14 | All | 1.37E-07 | 1.09 (1.06 - 1.12) | 6.29E-02 | 1.07 (1.00 - 1.15) | 1.74E-03 | 1.11 (1.04 - 1.19) | 1.25E-04 | 1.12 (1.06 - 1.18) |
| rs7068341 | 10 | 16674305 | T | 2.25E-06 | 1.09 (1.05 - 1.12) | 0.00 | 0.75 | 0.12 | All | 2.25E-06 | 1.09 (1.05 - 1.12) | 1.92E-01 | 1.05 (0.98 - 1.13) | 2.42E-03 | 1.11 (1.04 - 1.20) | 2.73E-02 | 1.07 (1.01 - 1.14) |
| rs2506155 | 10 | 33543185 | A | 3.30E-06 | 1.08 (1.04 - 1.11) | 0.00 | 0.72 | 0.15 | All | 3.30E-06 | 1.08 (1.04 - 1.11) | 5.57E-03 | 1.10 (1.03 - 1.17) | 1.03E-02 | 1.09 (1.02 - 1.16) | - | - |
| rs6479874 | 10 | 52459361 | T | 2.77E-07 | 1.09 (1.05 - 1.12) | 0.00 | 0.74 | 0.14 | All | 2.77E-07 | 1.09 (1.05 - 1.12) | 1.82E-01 | 1.05 (0.98 - 1.12) | 1.52E-02 | 1.08 (1.02 - 1.16) | 2.87E-03 | 1.09 (1.03 - 1.15) |
| rs11000137 | 10 | 53351800 | T | 2.86E-06 | 1.07 (1.04 - 1.10) | 0.00 | 0.70 | 0.17 | All | 2.86E-06 | 1.07 (1.04 - 1.10) | 7.24E-02 | 1.06 (0.99 - 1.13) | 2.02E-01 | 0.96 (0.91 - 1.02) | - | - |
| rs10763296 | 10 | 75444141 | G | 9.51E-06 | 1.05 (1.03 - 1.08) | 0.00 | 0.75 | 0.38 | All | 9.51E-06 | 1.05 (1.03 - 1.08) | 2.06E-01 | 1.03 (0.98 - 1.09) | - | - | - | - |
| rs7900239 | 10 | 80185087 | A | 8.74E-06 | 1.09 (1.05 - 1.13) | 0.00 | 0.73 | 0.10 | All | 8.74E-06 | 1.09 (1.05 - 1.13) | 3.36E-03 | 1.12 (1.04 - 1.22) | 7.25E-02 | 1.07 (0.99 - 1.16) | 2.33E-03 | 1.12 (1.04 - 1.20) |
| rs6583954 | 10 | 96524253 | T | 4.15E-06 | 1.08 (1.04 - 1.11) | 0.00 | 0.74 | 0.14 | All | 4.15E-06 | 1.08 (1.04 - 1.11) | 1.57E-02 | 1.08 (1.02 - 1.16) | 1.16E-01 | 1.05 (0.99 - 1.12) | - | - |
| rs11188403 | 10 | 97365258 | G | 9.73E-06 | 1.06 (1.03 - 1.08) | 0.00 | 0.63 | 0.32 | All | 9.73E-06 | 1.06 (1.03 - 1.08) | 2.20E-02 | 1.06 (1.01 - 1.12) | - | - | 8.00E-02 | 1.04 (1.00 - 1.09) |
| rs577969 | 10 | 100281166 | T | 4.11E-06 | 1.13 (1.07 - 1.19) | 0.00 | 0.65 | 0.05 | All | 4.11E-06 | 1.13 (1.07 - 1.19) | 1.59E-01 | 1.09 (0.97 - 1.23) | - | - | 8.96E-04 | 1.17 (1.07 - 1.28) |
| rs1890185 | 10 | 104738708 | G | 3.61E-07 | 1.06 (1.04 - 1.08) | 0.00 | 0.70 | 0.39 | All | 3.61E-07 | 1.06 (1.04 - 1.08) | 1.60E-03 | 1.08 (1.03 - 1.13) | - | - | 4.57E-02 | 1.04 (1.00 - 1.08) |
| rs10736184 | 10 | 107881592 | C | 1.68E-05 | 1.08 (1.04 - 1.12) | 0.00 | 0.66 | 0.12 | All | 1.68E-05 | 1.08 (1.04 - 1.12) | 9.57E-01 | 1.00 (0.93 - 1.07) | 5.37E-01 | 1.02 (0.95 - 1.10) | 1.17E-04 | 1.13 (1.06 - 1.20) |
| rs12355831 | 10 | 114192516 | G | 1.94E-06 | 1.09 (1.05 - 1.14) | 0.00 | 0.71 | 0.11 | All | 1.94E-06 | | | | | | | |

| Marker | | | | Lowest p-value | | | | | | All samples | | Clinics | | MA | | MO | |
|------------|-----|-----------|--------------|-----------------|--------------------|---------|----------------|------|--------|-------------|--------------------|-----------------|--------------------|----------|--------------------|----------|--------------------|
| SNP | Chr | Position* | Minor allele | Lowest p-value | OR (95% CI) | Q-value | r ² | MAF | Group | P-value | OR | P-value | OR | P-value | OR | P-value | OR |
| rs13063872 | 3 | 71547025 | A | 9.25E-06 | 0.80 (0.73 - 0.89) | 0.09 | 0.50 | 0.07 | Clinic | 7.25E-03 | 0.94 [0.90 - 0.98] | 9.25E-06 | 0.80 [0.73 - 0.89] | 3.62E-05 | 0.82 [0.75 - 0.90] | 3.43E-02 | 0.91 [0.84 - 0.99] |
| rs6549438 | 3 | 72243923 | A | 3.72E-06 | 0.89 (0.85 - 0.94) | 0.98 | 0.00 | 0.48 | Clinic | 3.41E-01 | 0.99 [0.97 - 1.01] | 3.72E-06 | 0.89 [0.85 - 0.94] | 2.05E-01 | 0.97 [0.93 - 1.02] | 3.54E-01 | 0.98 [0.94 - 1.02] |
| rs11726563 | 4 | 46518391 | C | 8.24E-06 | 0.86 (0.81 - 0.92) | 0.98 | 0.00 | 0.16 | Clinic | 1.32E-02 | 0.96 [0.93 - 0.99] | 8.24E-06 | 0.86 [0.81 - 0.92] | 4.72E-02 | 0.94 [0.88 - 1.00] | 1.19E-01 | 0.96 [0.90 - 1.01] |
| rs4478147 | 4 | 87692800 | G | 2.18E-06 | 1.12 (1.07 - 1.18) | 0.13 | 0.43 | 0.47 | Clinic | 2.69E-01 | 1.01 [0.99 - 1.03] | 2.18E-06 | 1.12 [1.07 - 1.18] | 1.06E-02 | 1.06 [1.01 - 1.11] | 7.56E-01 | 0.99 [0.96 - 1.03] |
| rs4704296 | 5 | 75538166 | G | 5.66E-06 | 0.90 (0.85 - 0.94) | 0.16 | 0.40 | 0.47 | Clinic | 9.24E-02 | 0.98 [0.96 - 1.00] | 5.66E-06 | 0.90 [0.85 - 0.94] | 1.89E-02 | 0.95 [0.91 - 0.99] | 3.58E-01 | 0.98 [0.94 - 1.02] |
| rs17608902 | 5 | 127744466 | A | 1.33E-07 | 1.25 (1.15 - 1.35) | 1.00 | 0.00 | 0.09 | Clinic | 1.14E-02 | 1.05 [1.01 - 1.09] | 1.33E-07 | 1.25 [1.15 - 1.35] | 8.59E-06 | 1.19 [1.10 - 1.28] | 6.30E-01 | 1.02 [0.95 - 1.09] |
| rs17570583 | 5 | 171491236 | A | 8.78E-06 | 1.23 (1.12 - 1.35) | 0.49 | 0.00 | 0.08 | Clinic | 4.25E-02 | 1.04 [1.00 - 1.09] | 8.78E-06 | 1.23 [1.12 - 1.35] | 1.11E-03 | 1.16 [1.06 - 1.26] | 5.38E-02 | 1.08 [1.00 - 1.16] |
| rs602848 | 6 | 131488484 | C | 1.40E-06 | 1.18 (1.10 - 1.26) | 0.60 | 0.00 | 0.16 | Clinic | 1.85E-03 | 1.05 [1.02 - 1.08] | 1.40E-06 | 1.18 [1.10 - 1.26] | 5.40E-06 | 1.16 [1.09 - 1.24] | 3.58E-01 | 1.03 [0.97 - 1.08] |
| rs12186141 | 6 | 154046664 | C | 4.12E-06 | 0.89 (0.85 - 0.94) | 0.53 | 0.00 | 0.44 | Clinic | 1.06E-02 | 0.97 [0.95 - 0.99] | 4.12E-06 | 0.89 [0.85 - 0.94] | 3.33E-02 | 0.95 [0.91 - 1.00] | 3.47E-01 | 0.98 [0.94 - 1.02] |
| rs11777116 | 8 | 24100246 | T | 6.48E-08 | 1.27 (1.17 - 1.39) | 0.30 | 0.18 | 0.08 | Clinic | 4.56E-03 | 1.07 [1.02 - 1.11] | 6.48E-08 | 1.27 [1.17 - 1.39] | 5.36E-05 | 1.19 [1.09 - 1.30] | 1.34E-01 | 1.07 [0.98 - 1.16] |
| rs4738393 | 8 | 56762331 | A | 6.29E-06 | 1.15 (1.08 - 1.22) | 0.20 | 0.33 | 0.33 | Clinic | - | - | 6.29E-06 | 0.87 [0.82 - 0.92] | 2.03E-04 | 0.89 [0.84 - 0.95] | 5.35E-03 | 0.93 [0.88 - 0.98] |
| rs400824 | 8 | 81520257 | T | 9.41E-06 | 0.89 (0.84 - 0.94) | 0.31 | 0.16 | 0.30 | Clinic | 9.85E-02 | 0.98 [0.96 - 1.00] | 9.41E-06 | 0.89 [0.84 - 0.94] | 5.59E-02 | 0.95 [0.91 - 1.00] | 2.39E-01 | 0.97 [0.93 - 1.02] |
| rs4493873 | 8 | 92144819 | A | 4.58E-06 | 1.14 (1.08 - 1.20) | 0.66 | 0.59 | 0.36 | Clinic | - | - | 4.58E-06 | 0.88 [0.83 - 0.93] | - | - | - | - |
| rs12552279 | 9 | 6684837 | C | 2.71E-06 | 1.25 (1.14 - 1.37) | 0.42 | 0.00 | 0.07 | Clinic | 4.85E-02 | 1.05 [1.00 - 1.10] | 2.71E-06 | 1.25 [1.14 - 1.37] | 2.08E-03 | 1.15 [1.05 - 1.26] | 1.90E-01 | 1.06 [0.97 - 1.16] |
| rs378563 | 9 | 9010223 | C | 7.53E-06 | 0.88 (0.83 - 0.93) | 0.02 | 0.66 | 0.23 | Clinic | 9.26E-01 | 1.00 [0.97 - 1.03] | 7.53E-06 | 0.88 [0.83 - 0.93] | 1.07E-01 | 0.95 [0.90 - 1.01] | 1.11E-01 | 0.96 [0.91 - 1.01] |
| rs6478241 | 9 | 11829429 | A | 1.04E-09 | 1.16 (1.11 - 1.22) | 0.65 | 0.00 | 0.38 | Clinic | 7.42E-07 | 1.06 [1.04 - 1.09] | 1.04E-09 | 1.16 [1.11 - 1.22] | 5.09E-03 | 1.07 [1.02 - 1.12] | 1.45E-07 | 1.12 [1.08 - 1.18] |
| rs2274491 | 10 | 97186968 | T | 6.67E-06 | 1.13 (1.07 - 1.19) | 0.53 | 0.00 | 0.32 | Clinic | - | - | 6.67E-06 | 0.89 [0.84 - 0.94] | 7.88E-04 | 0.92 [0.88 - 0.97] | - | - |
| rs12282928 | 11 | 48288604 | G | 8.84E-06 | 0.88 (0.83 - 0.93) | 0.83 | 0.00 | 0.23 | Clinic | 4.21E-02 | 0.98 [0.95 - 1.00] | 8.84E-06 | 0.88 [0.83 - 0.93] | 1.02E-01 | 0.96 [0.91 - 1.01] | 2.98E-01 | 0.98 [0.93 - 1.02] |
| rs10778070 | 12 | 99675606 | A | 9.84E-06 | 0.89 (0.85 - 0.94) | 0.07 | 0.54 | 0.33 | Clinic | 4.75E-01 | 0.99 [0.97 - 1.01] | 9.84E-06 | 0.89 [0.85 - 0.94] | 5.88E-04 | 0.92 [0.88 - 0.96] | 7.17E-01 | 0.99 [0.95 - 1.03] |
| rs17675602 | 16 | 81520246 | T | 5.46E-06 | 0.83 (0.76 - 0.90) | 0.08 | 0.52 | 0.13 | Clinic | - | - | 5.46E-06 | 1.21 [1.12 - 1.32] | 4.19E-01 | 1.03 [0.95 - 1.12] | 3.75E-02 | 1.00 [0.90 - 1.10] |
| rs473518 | 18 | 18338672 | T | 8.61E-06 | 1.21 (1.11 - 1.32) | 0.37 | 0.07 | 0.12 | Clinic | - | - | 8.61E-06 | 0.83 [0.76 - 0.90] | 1.31E-02 | 0.90 [0.83 - 0.98] | 1.61E-03 | 0.88 [0.82 - 0.95] |
| rs11874712 | 18 | 41942574 | A | 1.58E-07 | 1.15 (1.09 - 1.20) | 0.29 | 0.19 | 0.41 | Clinic | 4.83E-02 | 1.02 [1.00 - 1.05] | 1.58E-07 | 1.15 [1.09 - 1.20] | 3.35E-03 | 1.07 [1.02 - 1.13] | 1.06E-01 | 1.03 [0.99 - 1.08] |
| rs12480819 | 20 | 17540300 | G | 3.01E-06 | 1.15 (1.08 - 1.22) | 0.72 | 0.00 | 0.24 | Clinic | 2.20E-02 | 1.03 [1.00 - 1.06] | 3.01E-06 | 1.15 [1.08 - 1.22] | 4.67E-02 | 1.06 [1.00 - 1.12] | 1.55E-02 | 1.06 [1.01 - 1.11] |
| rs11986854 | 20 | 33847048 | A | 7.42E-06 | 1.17 (1.09 - 1.26) | 0.74 | 0.00 | 0.14 | Clinic | 5.09E-02 | 1.03 [1.00 - 1.07] | 7.42E-06 | 1.17 [1.09 - 1.26] | 1.86E-01 | 1.05 [0.98 - 1.12] | 1.25E-01 | 0.99 [0.99 - 1.12] |
| rs16985493 | 20 | 59276958 | A | 4.37E-06 | 1.37 (1.20 - 1.57) | 0.64 | 0.00 | 0.04 | Clinic | 1.23E-01 | 1.05 [0.99 - 1.11] | 4.37E-06 | 1.37 [1.20 - 1.57] | - | - | - | - |
| rs7528859 | 1 | 5583596 | A | 4.81E-06 | 1.12 (1.07 - 1.18) | 0.19 | 0.29 | 0.40 | MA | 1.11E-02 | 1.03 [1.01 - 1.06] | 2.34E-05 | 1.12 [1.06 - 1.18] | 4.81E-06 | 1.12 [1.07 - 1.18] | 7.24E-01 | 1.01 [0.96 - 1.05] |
| rs6693295 | 1 | 244289743 | T | 6.09E-06 | 1.14 (1.08 - 1.21) | 0.04 | 0.50 | 0.19 | MA | 2.63E-03 | 1.05 [1.02 - 1.08] | 9.05E-06 | 1.15 [1.08 - 1.23] | 6.09E-06 | 1.14 [1.08 - 1.21] | 2.59E-03 | 1.08 [1.03 - 1.14] |
| rs4345220 | 4 | 41334270 | A | 1.70E-06 | 1.14 (1.08 - 1.21) | 0.34 | 0.11 | 0.44 | MA | - | - | 2.34E-02 | 0.94 [0.89 - 0.99] | 1.70E-06 | 0.87 [0.83 - 0.92] | 1.45E-02 | 0.94 [0.89 - 0.99] |
| rs2159222 | 7 | 15724525 | T | 8.03E-06 | 0.86 (0.81 - 0.92) | 0.36 | 0.09 | 0.18 | MA | 3.58E-03 | 0.95 [0.92 - 0.98] | 1.96E-03 | 1.11 [1.04 - 1.19] | 8.03E-06 | 0.86 [0.81 - 0.92] | 1.64E-01 | 0.96 [0.91 - 1.02] |
| rs1364402 | 7 | 136234903 | C | 3.62E-06 | 0.84 (0.78 - 0.90) | 0.00 | 0.68 | 0.09 | MA | 1.34E-02 | 0.95 [0.92 - 0.99] | - | - | 3.62E-06 | 0.84 [0.78 - 0.90] | 2.27E-01 | 0.96 [0.90 - 1.03] |
| rs7015657 | 8 | 21011831 | G | 7.88E-08 | 1.15 (1.09 - 1.21) | 0.63 | 0.00 | 0.30 | MA | 5.91E-02 | 1.02 [1.00 - 1.05] | 1.18E-04 | 1.11 [1.05 - 1.18] | 7.88E-08 | 1.15 [1.09 - 1.21] | 7.96E-01 | 1.01 [0.96 - 1.05] |
| rs963265 | 9 | 72284355 | C | 1.06E-06 | 0.89 (0.85 - 0.93) | 0.79 | 0.00 | 0.40 | MA | 8.09E-03 | 0.97 [0.95 - 0.99] | 1.13E-02 | 0.94 [0.89 - 0.99] | 1.06E-06 | 0.89 [0.85 - 0.93] | 9.16E-01 | 1.00 [0.96 - 1.04] |
| rs10820447 | 9 | 98171865 | T | 5.84E-06 | 1.16 (1.09 - 1.23) | 0.48 | 0.00 | 0.16 | MA | 5.09E-03 | 1.04 [1.01 - 1.08] | 2.34E-03 | 1.11 [1.04 - 1.18] | 5.84E-06 | 1.16 [1.09 - 1.23] | 8.31E-02 | 1.05 [0.99 - 1.11] |
| rs2820651 | 10 | 1461765 | A | 4.02E-07 | 1.22 (1.13 - 1.31) | 0.00 | 0.75 | 0.10 | MA | 4.13E-04 | 1.07 [1.03 - 1.11] | 9.97E-04 | 1.15 [1.06 - 1.25] | 4.02E-07 | 1.22 [1.13 - 1.31] | 1.13E-02 | 1.09 [1.02 - 1.17] |
| rs1244181 | 10 | 8131383 | A | 1.71E-06 | 1.15 (1.09 - 1.22) | 0.00 | 0.70 | 0.21 | MA | - | - | 9.15E-02 | 0.95 [0.89 - 1.01] | 1.71E-06 | 0.87 [0.82 - 0.92] | - | - |
| rs10826566 | 10 | 29404703 | A | 3.56E-06 | 1.16 (1.09 - 1.23) | 0.01 | 0.62 | 0.17 | MA | 6.42E-03 | 1.04 [1.01 - 1.08] | 1.11E-03 | 1.11 [1.04 - 1.18] | 3.56E-06 | 1.16 [1.09 - 1.23] | - | - |
| rs2986961 | 10 | 30127365 | C | 5.15E-07 | 1.14 (1.08 - 1.20) | 0.00 | 0.73 | 0.26 | MA | 2.87E-03 | 1.04 [1.01 - 1.06] | 8.18E-02 | 1.05 [0.99 - 1.11] | 5.15E-07 | 1.14 [1.08 - 1.20] | 2.61E-01 | 1.03 [0.98 - 1.07] |
| rs2137920 | 10 | 49898644 | T | 1.14E-06 | 1.15 (1.09 - 1.22) | 0.00 | 0.72 | 0.18 | MA | - | - | 3.71E-03 | 1.09 [1.03 - 1.16] | 1.14E-06 | 1.15 [1.09 - 1.22] | 7.62E-03 | 0.93 [0.89 - 0.98] |
| rs12413355 | 10 | 117963587 | A | 2.86E-06 | 1.14 (1.08 - 1.20) | 0.11 | 0.39 | 0.22 | MA | - | - | 4.11E-03 | 0.92 [0.87 - 0.97] | 2.86E-06 | 0.88 [0.84 - 0.93] | - | - |
| rs2074193 | 12 | 46057696 | G | 4.94E-07 | 1.15 (1.09 - 1.21) | 0.25 | 0.22 | 0.21 | MA | 8.92E-03 | 1.04 [1.01 - 1.06] | 3.16E-03 | 1.09 [1.03 - 1.15] | 4.94E-07 | 1.15 [1.09 - 1.21] | 7.50E-01 | 0.99 [0.95 - 1.04] |
| rs17051917 | 13 | 34666789 | T | 8.59E-06 | 0.84 (0.78 - 0.91) | 0.54 | 0.00 | 0.11 | MA | 8.89E-03 | 0.95 [0.92 - 0.99] | 1.16E-02 | 0.90 [0.84 - 0.98] | 8.59E-06 | 0.84 [0.78 - 0.91] | 2.99E-01 | 0.97 [0.90 - 1.03] |
| rs11072158 | 15 | 68421763 | A | 2.86E-06 | 0.85 (0.79 - 0.91) | 0.80 | 0.00 | 0.15 | MA | 1.32E-01 | 0.97 [0.94 - 1.01] | 1.48E-03 | 0.89 [0.83 - 0.96] | 2.86E-06 | 0.85 [0.79 - 0.91] | 8.03E-01 | 0.99 [0.93 - 1.05] |
| rs7227892 | 18 | 44590700 | T | 2.10E-06 | 0.88 (0.84 - 0.93) | 0.71 | 0.00 | 0.28 | MA | 3.66E-01 | 0.99 [0.96 - 1.01] | 5.87E-04 | 0.91 [0.86 - 0.96] | 2.10E-06 | 0.88 [0.84 - 0.93] | 6.05E-01 | 0.99 [0.94 - 1.03] |
| rs12454023 | 18 | 54160584 | T | 8.01E-07 | 1.12 (1.07 - 1.18) | 0.74 | 0.00 | 0.50 | MA | 5.18E-02 | 0.98 [0.96 - 1.00] | 8.66E-04 | 0.92 [0.88 - 0.97] | 8.01E-07 | 0.89 [0.85 - 0.93] | 2.07E-01 | 0.97 [0.93 - 1.02] |
| rs973009 | 19 | 43866172 | G | 4.03E-06 | 0.85 (0.79 - 0.91) | 0.55 | 0.00 | 0.13 | MA | 4.64E-05 | 0.93 [0.90 - 0.96] | 4.19E-05 | 0.86 [0.81 - 0.93] | 4.03E-06 | 0.85 [0.79 - 0.91] | 6.27E-02 | 0.94 [0.89 - 1.00] |
| rs2076054 | 22 | 31162874 | C | 8.34E-06 | 0.89 (0.85 - 0.94) | 0.39 | 0.06 | 0.26 | MA | 1.18E-02 | 0.97 [0.95 - 1.00] | 1.24E-02 | 0.93 [0.89 - 0.99] | 8.34E-06 | 1.12 [1.07 - 1.18] | 8.05E-01 | 0.99 [0.95 - 1.04] |
| rs17301853 | 1 | 172819434 | T | 1.48E-06 | 0.86 (0.80 - 0.91) | 0.02 | 0.57 | 0.12 | MO | 5.81E-02 | 0.96 [0.93 - 0.99] | 6.56E-06 | 0.84 [0.78 - 0.91] | 1.76E-01 | 0.95 [0.89 - 1.02] | 1.48E-06 | 0.86 [0.80 - 0.91] |
| rs6693532 | 1 | 213021562 | C | 4.47E-06 | 1.10 (1.06 - 1.15) | 0.01 | 0.64 | 0.50 | MO | 5.81E-04 | 0.96 [0.94 - 0.98] | 2.53E-03 | 0.93 [0.88 - 0.97] | 1.07E-02 | 0.94 [0.90 - 0.99] | 4.47E-06 | 0.91 [0.87 - 0.95] |
| rs6733818 | 2 | 179854520 | G | 6.92E-06 | 1.10 (1.05 - 1.15) | 0.38 | 0.06 | 0.40 | MO | 2.22E-04 | 1.04 [1.02 - 1.07] | 3.39E-02 | 1.05 [1.00 - 1.11] | 9.88E-01 | 1.00 [0.95 - 1.05] | 6.92E-06 | 1.10 [1.05 - 1.15] |
| rs488884 | 5 | 29075878 | T | 1.13E-06 | 0.91 (0.87 - 0.94) | 0.33 | 0.13 | 0.50 | MO | 4.03E-05 | 0.95 [0.93 - 0.98] | 9.35E-03 | 0.94 [0.90 - 0.98] | 1.32E-01 | 0.97 [0.92 - 1.01] | 1.13E-06 | 0.91 [0.87 - 0.94] |
| rs16879308 | 5 | 51272083 | T | 2.30E-06 | 0.81 (0.74 - 0.88) | 0.51 | 0.00 | 0.06 | MO | 2.93E-02 | 0.95 [0.91 - 0.99] | 5.00E-03 | 0.86 [0.78 - 0.96] | 3.34E-01 | 0.95 [0.87 - 1.05] | 2.30E-06 | 0.81 [0.74 - 0.88] |
| rs7718446 | 5 | 145729728 | G | 3.98E-06 | 0.90 (0.86 - 0. | | | | | | | | | | | | |

Supplementary Table 5. Association results at previously reported migraine GWAS loci

| SNP | Gene | All studies | | | | Excluding original studies | | | |
|------------|-----------------------------|-------------|--------------|----------|----------|----------------------------|----------------|----------|----------|
| | | All | Clinic-based | MA only | MO only | All | Clinic studies | MA only | MO only |
| rs1835740 | <i>MTDH</i> ^a | 0.12217 | 1.44E-04 | 1.49E-04 | 0.447029 | 0.883 | 0.754 | 0.594 | 0.447 |
| rs10166942 | <i>TRPM8</i> ^b | 2.91E-12 | 6.39E-09 | 1.69E-06 | 1.21E-10 | 1.12E-04 | 2.73E-05 | 0.051 | 4.99E-07 |
| rs2651899 | <i>PRDM16</i> ^b | 4.34E-14 | 3.06E-04 | 2.54E-04 | 1.56E-05 | 8.10E-08 | 0.007 | 0.417 | 0.001 |
| rs11172113 | <i>LRP1</i> ^b | 3.94E-19 | 1.15E-06 | 1.11E-05 | 9.96E-11 | 4.08E-12 | 4.26E-04 | 0.005 | 2.74E-07 |
| rs3790455 | <i>MEF2D</i> ^c | 1.91E-08 | 1.35E-07 | 0.123199 | 1.42E-05 | 4.12E-05 | 0.036 | 0.123 | 0.139 |
| rs7640543 | <i>TGFBR2</i> ^c | 1.32E-05 | 1.54E-06 | 0.041888 | 1.05E-05 | 1.96E-03 | 0.021 | 0.042 | 0.025 |
| rs9349379 | <i>PHACTR1</i> ^c | 4.60E-08 | 2.22E-06 | 0.316306 | 2.81E-10 | 8.92E-05 | 0.089 | 0.316 | 1.56E-04 |
| rs6478241 | <i>ASTN2</i> ^c | 4.43E-07 | 1.04E-09 | 0.005093 | 1.45E-07 | 2.08E-04 | 1.12E-04 | 5.09E-03 | 3.07E-03 |

MA – migraine with aura. MO – migraine without aura. P-values for frequentist additive tests shown. Excluding original studies refers to the part of the study data independent of the original reports.

^a Excluding the Finnish, German and Dutch MA studies¹.

^b Excluding the Women's Genome Health Study and the Finnish, German and Dutch MA studies³.

^c Excluding the German and Dutch MO studies⁴.

Supplementary Table 6. SNP with the lowest P value at each locus in the analysed subgroups

| SNP | Chr | Position ^a | Location | Minor allele | Gene ^b | p-values | | | | |
|------------|-----|-----------------------|------------|--------------|--------------------|-----------------|-----------------|-----------------|----------|-----------------|
| | | | | | | All | Clinics | Population | MA | MO |
| rs2651899 | 1 | 3,073,572 | Genic | C | <i>PRDM16</i> | 4.34E-14 | 3.06E-04 | 3.30E-11 | 2.54E-04 | 1.56E-05 |
| rs10915437 | 1 | 4,082,866 | Intergenic | G | <i>near AJAP1</i> | 6.13E-04 | 2.81E-08 | 3.79E-01 | 1.56E-04 | 9.77E-01 |
| rs12134493 | 1 | 115,479,469 | Intergenic | A | <i>near TSPAN2</i> | 4.79E-14 | 1.19E-05 | 4.46E-10 | 6.19E-04 | 5.29E-08 |
| rs2274316 | 1 | 154,712,866 | Genic | C | <i>MEF2D</i> | 1.42E-08 | 1.43E-07 | 3.14E-04 | 8.66E-02 | 2.31E-05 |
| rs6741751 | 2 | 234,492,400 | Genic | A | <i>TRPM8</i> | 9.11E-14 | 1.09E-08 | 4.97E-08 | 1.03E-07 | 8.64E-11 |
| rs6790925 | 3 | 30,455,089 | Intergenic | T | <i>near TGFBR2</i> | 8.74E-05 | 2.16E-08 | 1.35E-01 | 1.54E-02 | 8.35E-05 |
| rs9349379 | 6 | 13,011,943 | Genic | G | <i>PHACTR1</i> | 4.60E-08 | 2.22E-06 | 4.15E-04 | 3.16E-01 | 2.81E-10 |
| rs11759769 | 6 | 97,171,933 | Genic | A | <i>FHL5</i> | 1.34E-11 | 4.22E-07 | 6.35E-07 | 5.69E-04 | 1.58E-12 |
| rs4379368 | 7 | 40,432,725 | Genic | T | <i>c7orf10</i> | 1.07E-09 | 7.18E-07 | 2.15E-05 | 1.24E-03 | 5.81E-08 |
| rs10504861 | 8 | 89,617,048 | Intergenic | T | <i>near MMP16</i> | 0.003528 | 1.87E-02 | 0.042 | 0.185 | 1.17E-08 |
| rs17220352 | 9 | 118,287,880 | Genic | G | | 5.46E-09 | 1.16E-07 | 1.83E-04 | 1.10E-02 | 1.49E-07 |
| rs6478241 | 9 | 118,292,450 | Genic | A | <i>ASTN2</i> | 4.43E-07 | 1.04E-09 | 1.58E-02 | 5.09E-03 | 1.45E-07 |
| rs11172113 | 12 | 55,813,550 | Genic | C | <i>LRP1</i> | 3.94E-19 | 1.15E-06 | 4.50E-14 | 1.11E-05 | 9.96E-11 |

Chr – chromosome, Clinics – only cases recruited from headache clinics used, Population – samples from population cohorts, MA – migraine with aura, MO – migraine without aura. Bold text indicates genome-wide significant results. N.B. analysis for MA and MO are not independent, because they use some overlapping controls.

Supplementary Table 7. Odds ratios for the SNP with the lowest P value at each locus in the analysed subgroups

| SNP | Chr | Position ^a | Location | Minor allele | Gene ^b | Odds ratios | | | | |
|------------|-----|-----------------------|------------|--------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| | | | | | | All | Clinics | Population | MA | MO |
| rs2651899 | 1 | 3,073,572 | Genic | C | <i>PRDM16</i> | 1.09 [1.07 - 1.11] | 1.09 [1.04 - 1.15] | 1.09 [1.06 - 1.12] | 1.09 [1.04 - 1.14] | 1.09 [1.05 - 1.14] |
| rs10915437 | 1 | 4,082,866 | Intergenic | G | <i>near AJAP1</i> | 0.96 [0.93 - 0.98] | 0.86 [0.82 - 0.91] | 0.99 [0.96 - 1.02] | 0.90 [0.86 - 0.95] | 1.00 [0.96 - 1.05] |
| rs12134493 | 1 | 115,479,469 | Intergenic | A | <i>near TSPAN2</i> | 1.14 [1.10 - 1.18] | 1.18 [1.10 - 1.27] | 1.13 [1.09 - 1.17] | 1.13 [1.05 - 1.21] | 1.18 [1.11 - 1.26] |
| rs2274316 | 1 | 154,712,866 | Genic | C | <i>MEF2D</i> | 1.07 [1.05 - 1.10] | 1.14 [1.09 - 1.20] | 1.05 [1.02 - 1.08] | 1.04 [0.99 - 1.10] | 1.10 [1.05 - 1.15] |
| rs6741751 | 2 | 234,483,608 | Genic | A | <i>TRPM8</i> | 0.87 [0.84 - 0.90] | 0.79 [0.73 - 0.86] | 0.89 [0.85 - 0.93] | 0.81 [0.75 - 0.88] | 0.80 [0.75 - 0.86] |
| rs6790925 | 3 | 30,455,089 | Intergenic | T | <i>near TGFBR2</i> | 1.05 [1.02 - 1.07] | 1.15 [1.10 - 1.21] | 1.02 [0.99 - 1.05] | 1.06 [1.01 - 1.11] | 1.09 [1.04 - 1.13] |
| rs9349379 | 6 | 13,011,943 | Genic | G | <i>PHACTR1</i> | 0.93 [0.91 - 0.96] | 0.89 [0.85 - 0.93] | 0.95 [0.92 - 0.98] | 0.97 [0.93 - 1.03] | 0.86 [0.82 - 0.90] |
| rs11759769 | 6 | 96,967,075 | Genic | A | <i>FHL5</i> | 1.10 [1.07 - 1.13] | 1.16 [1.09 - 1.23] | 1.08 [1.05 - 1.11] | 1.10 [1.04 - 1.16] | 1.18 [1.13 - 1.24] |
| rs4379368 | 7 | 40,432,725 | Genic | T | <i>c7orf10</i> | 1.11 [1.08 - 1.15] | 1.20 [1.12 - 1.29] | 1.09 [1.05 - 1.13] | 1.12 [1.05 - 1.20] | 1.19 [1.12 - 1.27] |
| rs10504861 | 8 | 89,617,048 | Intergenic | T | <i>near MMP16</i> | 0.96 [0.93 - 0.99] | 0.93 [0.87 - 0.99] | 0.97 [0.93 - 1.00] | 0.96 [0.91 - 1.02] | 0.86 [0.81 - 0.90] |
| rs17220352 | 9 | 118,287,880 | Genic | G | <i>ASTN2</i> | 1.08 [1.05 - 1.11] | 1.16 [1.10 - 1.23] | 1.06 [1.03 - 1.09] | 1.14 [1.09 - 1.20] | 1.07 [1.02 - 1.14] |
| rs6478241 | 9 | 118,292,450 | Genic | A | | 1.06 [1.04 - 1.09] | 1.16 [1.11 - 1.22] | 1.03 [1.01 - 1.06] | 1.07 [1.02 - 1.12] | 1.12 [1.08 - 1.18] |
| rs11172113 | 12 | 55,813,550 | Genic | C | <i>LRP1</i> | 0.90 [0.88 - 0.92] | 0.89 [0.84 - 0.93] | 0.91 [0.88 - 0.93] | 0.90 [0.86 - 0.94] | 0.87 [0.84 - 0.91] |

Chr – chromosome, Clinics – only cases recruited from headache clinics used, Population – samples from population cohorts, MA – migraine with aura, MO – migraine without aura. The intensity of the shading corresponds to the magnitude of the odds ratio. Shades of blue indicate lowered OR and red increased OR. All odds ratios standardized for the minor allele. N.B. analysis for MA and MO are not independent, because they use some overlapping controls.

Supplementary Table 8. SNPs at the loci significantly associated with migraine expected to affect transcription factor binding sites

| Chr | Position | SNP | RegulomeDB score |
|-----|-------------|------------|--|
| 6 | 96,853,578 | rs6924957 | eQTL + TF binding / DNase peak |
| 12 | 57,533,689 | rs4759277 | eQTL + TF binding / DNase peak |
| 12 | 57,534,469 | rs1466535 | eQTL + TF binding / DNase peak |
| 1 | 156,446,449 | rs12131289 | TF binding + matched TF motif + matched DNase Footprint + DNase peak |
| 12 | 57,532,748 | rs1385526 | TF binding + matched TF motif + matched DNase Footprint + DNase peak |
| 1 | 3,087,372 | rs10909887 | TF binding + any motif + DNase Footprint + DNase peak |
| 1 | 156,446,241 | rs2274316 | TF binding + any motif + DNase Footprint + DNase peak |
| 2 | 234,821,529 | rs11563063 | TF binding + any motif + DNase Footprint + DNase peak |
| 8 | 89,566,902 | rs1352318 | TF binding + matched TF motif + DNase peak |

List of SNPs at migraine-associated loci expected to change transcription factor binding according to the ENCODE data at RegulomeDB (<http://regulome.stanford.edu>; showing SNPs with RegulomeDB scores of 2f or higher). All basepair positions are given in build 36/hg18. Chr – chromosome. TF – transcription factor.

Supplementary Table 9. Heterogeneity analysis comparing the results from a fixed effects model and a random effects model between MA and MO

| Chr | Position | SNP | EA | EAF | OR | | | p-value | | | | |
|-----|------------|-----------|----|------|------|------|------|----------|----------|----------|----------|----------|
| | | | | | All | MA | MO | MA | MO | FEM | REM | Het. |
| 6 | 13,011,943 | rs9349379 | G | 0.40 | 1.10 | 1.03 | 1.17 | 0.32 | 2.81E-10 | 1.30E-07 | 1.33E-09 | 3.21E-04 |
| 6 | 29,715,025 | rs3095267 | C | 0.19 | 0.95 | 1.03 | 0.89 | 0.27 | 8.53E-06 | 8.69E-03 | 2.69E-05 | 1.70E-04 |
| 6 | 30,845,465 | rs3094117 | C | 0.23 | 1.05 | 0.97 | 1.12 | 0.23 | 1.54E-06 | 4.79E-03 | 4.62E-06 | 4.64E-05 |
| 8 | 21,011,831 | rs7015657 | G | 0.30 | 0.94 | 0.87 | 0.99 | 7.88E-08 | 0.80 | 1.90E-04 | 5.18E-07 | 1.08E-04 |
| 9 | 22,016,077 | rs615552 | C | 0.43 | 1.04 | 0.98 | 1.10 | 0.31 | 3.64E-06 | 5.07E-03 | 1.29E-05 | 1.30E-04 |
| 9 | 72,284,355 | rs963265 | C | 0.40 | 0.95 | 0.89 | 1.00 | 1.06E-06 | 0.92 | 1.07E-03 | 6.57E-06 | 2.90E-04 |
| 12 | 46,057,696 | rs2074193 | G | 0.21 | 1.06 | 1.15 | 0.99 | 4.94E-07 | 0.75 | 1.87E-03 | 3.01E-06 | 7.31E-05 |

EA – effect allele. EAF – effect allele frequency. MA – migraine with aura. MO – migraine without aura. FEM – fixed effects model. REM – random effects model. Het. – *P* value for the heterogeneity test.

Supplementary Table 10. Pathways associating in the gene set enrichment analysis (GSEA) with a FDR *P* value<0.2 in the MAGENTA analysis

| Phenotype | Pathway | GSEA p-value | FDR | Expected | Observed |
|--------------|--|--------------|----------|----------|----------|
| All migraine | - | - | - | - | - |
| Clinics only | oxygen binding | 6.70E-05 | 1.05E-01 | 8 | 19 |
| MO only | glycogen catabolic process | 5.00E-04 | 1.02E-01 | 2 | 6 |
| MO only | traversing start control point of mitotic cell cycle | 6.00E-04 | 1.97E-01 | 2 | 6 |
| MA only | nervous system development | 1.50E-05 | 1.83E-01 | 84 | 117 |

Showing only pathways associated with a gene set enrichment analysis (GSEA) *P* value less than 0.2. Expected – expected number of genes below FDR threshold in the pathway. Observed – observed number of genes below the FDR threshold in the pathway. MO – migraine without aura. MA – migraine with aura.

Supplementary Table 11. Genes highlighted by DAPPLE analysis due to significant connectivity

| Gene | P-value |
|-----------------|----------|
| <i>SLC43A2</i> | 0.001997 |
| <i>TRIM28</i> | 0.001997 |
| <i>CDC5L</i> | 0.001997 |
| <i>C7orf10</i> | 0.001997 |
| <i>ZNF709</i> | 0.003992 |
| <i>ATP5B</i> | 0.005979 |
| <i>ZNF311</i> | 0.009945 |
| <i>SRSF3</i> | 0.009945 |
| <i>SMYD5</i> | 0.011922 |
| <i>SLC35F2</i> | 0.011934 |
| <i>KRT10</i> | 0.013896 |
| <i>LRRC47</i> | 0.015873 |
| <i>C19orf29</i> | 0.015888 |
| <i>DHX16</i> | 0.021857 |
| <i>GEMIN4</i> | 0.023714 |
| <i>TPPP3</i> | 0.035429 |

Supplementary Table 12. Results of the GRAIL analysis

| GENE | GRAIL p-value | Similar genes (overall rank) |
|-----------------|---------------|--|
| <i>PHACTR1</i> | 0.001034526 | <i>NRP1</i> (4), <i>C8orf79</i> (68), <i>ASTN2</i> (79), <i>FRMD4A</i> (93), <i>ARL15</i> (94), <i>PPP1R11</i> (130), <i>PTPRD</i> (172), <i>FARP1</i> (186), <i>RBM39</i> (195) |
| <i>AS3MT</i> | 0.013316371 | <i>SMYD3</i> (12), <i>CDKN2B</i> (85), <i>SUV39H2</i> (92), <i>CYP2C18</i> (110), <i>CYP2C8</i> (178) |
| <i>USMG5</i> | 0.018108738 | <i>ATP5A1</i> (4), <i>FAM49B</i> (70), <i>KIAA0776</i> (114) |
| <i>RASSF5</i> | 0.020942561 | <i>RSU1</i> (22), <i>KSR2</i> (41), <i>CASZ1</i> (123), <i>SMYD3</i> (162), <i>KANK1</i> (184), <i>CDKN2B</i> (192) |
| <i>C10orf88</i> | 0.022462479 | <i>FAM49B</i> (12), <i>ARL15</i> (111), <i>SNX24</i> (151) |

Results of the GRAIL analysis, detailing the genes at each significant locus with the most significantly associated other genes based on text-mining of literature abstracts.

Supplementary Note

Comparing the subgroup results

Since an extensive discussion in the migraine field has concerned whether MA and MO are distinct subtypes or part of the same spectrum (e.g. ¹⁶ and ¹⁷), we conducted two exploratory analyses between the two subgroups. As fairly robust study sizes from both migraine subtypes were available, we conducted a heterogeneity analysis¹⁸ at the 146 reported loci (see **Methods**) to look for quantitative differences between the two main types of migraine, MA and MO. By requiring a significance threshold consistent with multiple hypothesis testing ($p < 0.00034$ [$=0.05/146$ tests]),

significant heterogeneity P values between MA and MO were subsequently observed at only seven loci. At these loci, employing a random effects model produced more significant P values than the fixed effects model (**Supplementary Table 9**). In addition, we performed an analysis comparing the effect sizes between the MO and MA subgroups. Of the 146 index SNPs for the 12 reported loci, 135 were present in both subgroups and 122 had the same effect direction. Of these 122 SNPs, 62 (51%) had a larger effect size in MA cases compared to MO cases, which does not differ significantly from that expected by chance (two-tailed binomial test $P = 0.928$). While some confounding can be introduced by the different level of difficulty in accurately diagnosing the two forms of migraine, and though significant heterogeneity was observed at a few loci, neither analysis points to clear differences between the two subtypes across these 146 loci. At the 12 significant loci, with the exception of *PHACTR1* (where significant heterogeneity was observed), and near *AJAP1* (where effect size is stronger in the MA group, but the heterogeneity test is not significant, heterogeneity $P = 0.004$), it similarly appears that for common risk variants, MO and MA appear to have a similar genetic loading in terms of liability. However, unlike in the secondary loci, among the 12 significant loci a trend for higher effect sizes in the MO group can be observed, leading to the difference between observed significant loci (**Fig. 2c, d**).

A heterogeneity analysis was also conducted to examine potential effect heterogeneity between men and women. None of the 146 index SNPs displayed genome-wide significant gender heterogeneity (data not shown). The strongest gender disparity was observed at marker rs12153243 on 5q31, with a gender heterogeneity P value of 0.004. For each locus where significant heterogeneity between MA and MO was observed, the locus was associated to MO but not MA.

The finding that the index SNPs in the identified loci have more extreme effect sizes in the clinical compared with population-based cohorts (**Supplementary Fig. 5, Supplementary Table 7**) may reflect enrichment of these variants in particularly severe and possibly differentiated subclasses of migraine cases that may be referred for clinic-based care. However, while the benefits of more in-depth phenotyping of the clinic-originated cases (who have, for example, been ascertained for familial aggregation of migraine) may be useful in future studies addressing rare variation, especially in individuals without the identified common genetic risk factors, the relative uniformity of effect sizes across both clinic- and population-based studies suggests that a questionnaire-based approach on larger numbers may yield greater short-term gain for genetic studies of migraine. This agrees with a number of previous studies where a high degree of specificity and sensitivity for diagnosing migraine via well-designed questionnaires (e.g. FMSQ(fs)¹⁹, DMQ3²⁰, and the Women's Health Study questionnaire²¹) has been demonstrated. In the participating study samples in general, self-reported

migraine has had high concordance when compared to diagnosis made by a headache specialist (see **Supplementary Note** for additional details). However, the lack of findings in the migraine with aura subgroup may suggest that accurately diagnosing aura based on questionnaire data is less successful.

Pathway analyses

We further analysed all 146 loci with a P value $< 1 \times 10^{-5}$ using pathway analysis methods (MAGENTA Gene Set Enrichment Analysis²²) as well as protein-protein interactions (DAPPLE²³) and text-mining (GRAIL²⁴). For all pathway analyses, the whole interval containing SNPs with P values below the reporting threshold (1×10^{-5}), plus 50 kb into each direction, was taken forward, as recommended by the analysis packages. In the MAGENTA analysis, no significant network enrichment was observed (**Supplementary Table 10**), as multiple non-overlapping pathways were among the most associated results, suggesting the genetic susceptibility to migraine is not mediated by any single known pathway. The pathway with the lowest P value was “Nervous system development”, with an FDR-corrected P value of 0.183. In the DAPPLE analysis, 13 individual genes were significantly more connected to other genes in the reported loci than we would expect by chance ($\text{FDR} < 0.05$), including *ATP5B* (also identified in the eQTL analysis); (**Supplementary Table 11**). Additionally, two of the significant genes (*LRP1* and *MMP16*) show strong evidence of direct connectivity (**Supplementary Fig. 10a**). The overall network was not statistically significant (Seed direct degrees P value 0.78, indirect degrees P value 0.07; **Supplementary Fig. 10b**). While DAPPLE has successfully identified pathways involved in e.g. common autoimmune disorders^{23,25}, it is possible that the coverage of protein-protein interaction data in the InWeb dataset²⁶ representing neuronal pathways involved in migraine is currently inadequate to map these molecular processes. In the GRAIL analysis, five genes (e.g. *PHACTR1*, which included *ASTN2* among the most similar genes) showed significant similarity to genes from other reported loci (**Supplementary Table 12**).

Cohort Descriptions

Participating population-based cohorts

ALSPAC

The Avon Longitudinal Study of Parents and Children (ALSPAC)²⁷ is a population-based birth cohort initially comprising of 14,541 mothers and their children recruited in the former County of Avon, UK between 1991 and 1992. Mothers indicated history of migraine via questionnaire during early pregnancy. Subjects were asked 'Have you ever had any of the following problems: migraine'. Controls subjects indicated the option "No never" and case subjects indicated either options "Yes had it recently" or "Yes in the past, not now".

Centre National de Génotypage (CNG) carried out DNA genotyping on the Illumina human660W-quadrant array and genotypes were called with Illumina GenomeStudio. PLINK (v1.07) was used to carry out quality control measures on an initial set of 10,015 subjects and 557,124 directly genotyped SNPs. SNPs were removed if they displayed more than 5% missingness or a Hardy-Weinberg equilibrium P -value of less than 1.0×10^{-6} . Additionally SNPs with a minor allele frequency of less than 1% were removed. Samples were excluded if they displayed more than 5% missingness, had indeterminate X chromosome heterozygosity or extreme autosomal heterozygosity. Samples showing evidence of population stratification were identified by multidimensional scaling of genome-wide IBS pairwise distances using the four HapMap populations as a reference, and then excluded. Cryptic relatedness was assessed, in PLINK, using a π -hat of more than 0.125 which is expected to correspond to roughly 12.5% alleles shared IBD or a relatedness at the first cousin level.

8,340 subjects and 526,688 SNPs passed these quality control filters. We imputed autosomal SNPs against the HapMap CEU population (release 22) using MaCH (v1.0.16). A combination of MaCH and Minimac (v4.4.3) was used to impute X chromosome genotypes against the HapMap CEU population (release 21). Genome-wide SNP data was analysed in a logistic regression in mach2dat (v1.0.18).

Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees.

Australian Twin cohort

The Australian Twin Migraine (ATM) GWA study includes data from Australian twins and their families. All cases and controls included in this study were unrelated individuals; one individual was selected from each family. The cases ($N = 1,683$; 466 [28%] male, 1,217 [72%] female) were preferentially selected from each family based on migraine severity. The population controls ($N = 2,383$; 1,225 [51%] male, 1,158 [49%] female) were randomly selected from families containing no known migraine cases. For the current study, two subsets of cases were identified: ATM1 encompassing 886 IHS MO cases (154 [17%] male, 732 [83%] female); and ATM2: encompassing 797 self-report (migraine "yes" or "no") cases (312 [39%] male, 485 [61%] female). To allow for potential differences in genetic risk for the different migraine definitions, we utilized a stratified analysis approach where the ATM1 and ATM2 cases were compared to a random selection of 1,586 and 797 of the 2,393 population controls, respectively. The mean age at interview was 37.5 years ($SD = 11.3$). All subjects gave informed consent and approval to conduct the research was obtained from the QIMR Human Research Ethics Committee.

Case and control individuals were drawn from our QIMR GWA cohort of over 19,000 individuals genotyped using a variety of Illumina GWA arrays. After strict QC, the observed genotypes were imputed up to HapMap2 (release 22) using the MaCH program²⁸. Association

analysis of allelic dosage scores within a logistic regression framework including sex and strata (ATM1/ATM2) as covariates was performed using the PLINK program²⁹. For a detailed description of the QIMR 19K GWA cohort, including QC and imputation methodology, see Medland et al. (2009)³⁰.

British 1958 Birth Cohort (B58C)

The British 1958 birth cohort is an ongoing follow-up of all persons born in England, Scotland and Wales during one week in 1958³¹. At age 33 years, a history of migraine ever was obtained by interview, whereas at 23 years of age, cohort members had been asked whether they had had migraine or recurrent sick headaches since their 16th birthday. For the purpose of this meta-analysis, cases were defined by a positive interview response for migraine ever at age 33. Controls were defined as cohort members who denied migraine ever at age 33, and reported no migraine or recurrent sick headaches since 16, when interviewed at age 23. Subjects who reported migraine or headaches between 16 and 23, but no history of migraine at age 33, were excluded from the analysis.

At the age of 44-45 years, the participants were followed up with a biomedical examination and blood sampling³², from which a DNA collection was established as a nationally representative reference panel (<http://www.b58cgene.sgul.ac.uk/>). Three non-overlapping subsets of the DNA collection were genotyped as part of case-control studies by the Wellcome Trust Case-Control Consortium³³, the Type 1 Diabetes Genetics Consortium³⁴ and the GABRIEL asthma genetics consortium³⁵. Imputations were performed using the HapMap release 21 CEU haplotypes by the MACH software²⁸. Within-cohort logistic regression analyses for migraine were performed using ProbABEL³⁶.

DeCODE

Icelandic individuals suffering from migraine were recruited from three sources: (1) a list of patients provided by two neurologists (401 potential participants), (2) responses to an advertisement in the newsletter of the Icelandic Migraine Society (137 participants), and (3) responses to a brief screening questionnaire mailed to a random sample of 20,000 Icelanders, aged 18–50 years and living in the Reykjavik area. All recruits were diagnosed based on their answers to the third edition of the deCODE Migraine Questionnaire (DMQ3) for use in genetic studies²⁰. The DMQ3 is a comprehensive migraine questionnaire that was designed based on ICHD-II¹⁵, and validated using a semi-structured, physician-conducted telephone interview as a gold standard. Approval for these studies was provided by the National Bioethics Committee and the Icelandic Data Protection Authority, and informed consent was obtained from all participants.

ERF

The Erasmus Rucphen Family (ERF) genetic isolate study is a family-based study in a genetically isolated population in the Southwest of the Netherlands. This young genetic isolate was founded in the mid-18th century and minimal immigration and marriages occurred between surrounding settlements due to social and religious reasons. The ERF population includes 3,465 individuals that are living descendants of 22 couples with at least six children baptized in the community church around 1850–1900. The subjects were unselected with respect to phenotypes. Details about the extensive genealogy and pedigree of the population are described elsewhere³⁷. Migraine was diagnosed using a validated three-stage screening method that included a telephone interview³⁸, which was based on the ICHD-II criteria¹⁵. The screening procedure is described in detail by Stam and colleagues³⁹. In brief, all participants filled out a concise screening questionnaire on headache and aura symptoms. Then, screen-positives received a detailed extended questionnaire. Finally, screen-

positives were telephone interviewed to further clarify their clinical symptoms by trained physicians who are experienced in diagnosing migraine patients. Final diagnosis was only made after the telephone interview and in consultation with a neurologist specialized in headache (GMT). The control group consisted of ERF participants negative for migraine based on the written three-stage screening procedure. The genome-wide association (GWA) study for migraine includes data from 1546 ERF participants; 330 migraineurs (189 MO and 141 MA) and 1216 controls. Of the cases, 81 (25%) were male and 249 (75%) were female; of the controls, 615 (51%) were male and 601 (49%) were female.

FinnTwin

The FinnTwin16 subsample included Finnish twins born 1975-79 and migraine was measured by a postal questionnaire (wave 4) when the twins were, on average, 25 years of age (range 22-27 years)⁴⁰. The twins were asked whether a physician had ever told them they had migraine. The type of migraine, symptoms and medication were not asked. The FinnTwin12 subsample included twins born in 1983-1987 and migraine was assessed as part of a structured interview by trained research nurses during a day-long clinical study when they were, on average, 22.4 years of age (range 20-25 years)⁴¹. They were asked whether they had migraine, whether the diagnosis was made by a health professional and the year it had been made. Medications were asked and coded. Migraine subtypes were not investigated.

HUNT

The 1,608 Norwegian migraine cases were recruited from the Nord-Trøndelag Health Study (HUNT), in which all inhabitants (age ≥ 20 years) of the Nord-Trøndelag county of Norway were invited to participate. Participants answered 13 headache questions designed to diagnose migraine according to a modified version of the ICHD criteria⁴², and to differentiate migraine with and without visual aura. This questionnaire-based classification has been validated by interview diagnoses, yielding positive and negative predictive values for ICHD migraine of 87% and 75% respectively⁴². The 1,097 Norwegian control samples were recruited from the same HUNT population study (see description above), and included 389 samples previously genotyped as part of a GWA study of lung cancer⁴³ and 572 samples genotyped as part of an ongoing GWA study of pre-eclampsia, in addition to 136 control samples genotyped for the present study. Participants fulfilling criteria for migraine were excluded from the control population.

NTR/NESDA

The NTR/NESDA cohort includes participants of the Netherlands Twin Registry (NTR) and the Netherlands Study of Depression and Anxiety (NESDA). Data collection procedures for these studies are described in detail elsewhere^{44,45}. Migraine was assessed with a questionnaire that provided information on the symptoms listed in the ICHD-II criteria. The questionnaire started with a screening question ("do you ever experience headache attacks, for instance migraine?"). Individuals screening positive subsequently answered a set of more detailed questions on their headache symptomatology. Based on these symptom data, a diagnosis was made, following the ICHD-II criteria¹⁵. Details on this procedure can be found in previous work⁴⁶.

Genotyping was performed on the Affymetrix 6.0 (N=298), Affymetrix Perlegen 5.0 (N=3,697), Illumina 370 (N=290), Illumina 660 (N=1,439) and Illumina Omni Express 1M (N=455) platforms. Calls were made with the platform specific software (Genotyper, Beadstudio). Per platform the quality control thresholds for SNPs were MAF > 1%, HWE > 0.00001, call rate >95% and

0.30 < heterozygosity < 0.35. Samples were excluded from the data if their expected sex and IBD status did not match, or if the genotype missing rate was above 10%. For each platform all SNPs were aligned to the positive strand of the HapMap 2 Build 36 release 24 CEU reference set. The alignment was checked using individuals and family members tested on multiple platforms. SNPs were excluded per platform if allele frequencies differed more than 15% with the reference set and/or the other platforms. The data of the platforms were subsequently merged into a single dataset (N=5,856). This merged set was imputed against the reference set using IMPUTE v2. After imputation, genotype dosage was calculated if the highest genotype probability was above 90%. Badly imputed SNPs were removed based on HWE < 0.00001, proper info < 0.40, MAF < 1%, allele frequency difference > 0.15 against reference. Among the NTR participants, related individuals were included in the sample. For the present analyses, unrelated individuals were selected from the sample by including one individual from each NTR family. To maximize the number of migraine cases, the individual with (the most severe) migraine was selected from families with one or more migraineurs. Furthermore, a subset of the NTR/NESDA cohort was originally genotyped for a study on major depressive disorder (MDD)⁴⁷, and therefore included MDD patients. Because of the known comorbidity of migraine and MDD, all MDD patients were excluded from the current analyses. The resulting selection included 282 migraine cases (42 males [15%], 240 females [85%], mean age 44.7, SD = 13.3) and 2,260 controls (1,012 males [45%], 1,248 females [55%], mean age 49.3, SD = 14.2). The association analyses were performed using SNPTEST (v 2.1.1)⁴⁸.

NFBC1966

Mothers expected to give birth in the two Northern provinces of Oulu and Lapland in 1966 were enrolled in the NFBC1966⁴⁹ (N = 12,058 live births). Primary clinical data collection on parents and the child occurred prenatally and at birth. Data collection on the child continued at ages six months, one year, 14 years (no data from one year or 14 years are included in this paper), 31 years, with assessment of a wide range of trait measures. Cohort members still living in Northern Finland and those who had moved to the capital area were invited to a clinical examination at age 31 years (N = 8,463). The attendees (71% response rate, N = 6,007) were adequately representative of the original cohort⁵⁰. Migraine was assessed based on the health questionnaire survey provided by the participants. The study was originally genotyped for the study⁵¹.

Rotterdam

This sample included participants of the Rotterdam Study, a prospective population based cohort study among persons 55 years or older who were living in Ommoord, a well-defined district of Rotterdam, the Netherlands⁵². The aim of this study was to investigate causes of frequent chronic diseases, with a focus on cardiovascular, neurologic, psychiatric, and ophthalmic diseases. The Medical Ethics Committee of Erasmus Medical Center approved of the study. The original cohort of the Rotterdam Study (7,983 participants) was expanded in 2000 (N = 3,011) and again in 2006 to include 3,932 persons who were 45 years of age or older. At study entry all participants underwent a structural interview and a physical examination, which was repeated every 3-4 years. The migraine questionnaire was introduced into the core study protocol in 2006 (response rate of 64.8%). For the current report, we used data from persons from the second cohort expansion (2006 to 2008) who completed the migraine questionnaire. Migraine data were available for 1,998 unrelated individuals, including 349 cases (79 male, 270 female) and 1,649 controls (805 male, 844 female). The mean age of the sample was 55.37 years (SD=4.51).⁵³

Twins UK

The study population comprised 4,809 individuals (428 males and 4,381 females) from the TwinsUK Adult Twin Registry⁵⁴. The twins were volunteers recruited through a national media campaign (www.twins.ac.uk), were not enriched for any particular disease or trait and were representative of the British general population⁵⁴. Volunteers provided informed consent and were administered a protocol approved by the St. Thomas' Hospital ethics committee. The twins were aged between 16 and 82 years with a standard deviation of 13 years and a mean age of 50 years. Migraine status was ascertained through questionnaires. 703 of the study participants fulfilled the IHS definition of migraine¹⁵, and of these, 235 with typical aura with migraine headache. Samples were genotyped with a combination of Illumina arrays (HumanHap300, and HumanHap610Q). The genotype data was imputed with IMPUTE⁵⁵ version 2 using HapMap2, release 22, combined CEU+YRI+ASN panels and the 610Q data was used as a reference panel for the HumanHap300 data. The imputed genotype data was analyzed with GWAF (Genome-wide association analyses for family data) to test for SNP association with adjustments for age⁵⁶. We used the equations option for logistic regression via generalized estimating of the GWAF software, which incorporates familial clustering.

Women's Genome Health Study

The Women's Genome Health Study (WGHS) is a prospective cohort of initially apparently healthy, female US health care professionals who were at least 45 years old at baseline, representing 72% of participants in the Women's Health Study (WHS) who provided a blood sample at baseline and consent for blood-based analyses. The WHS was a randomized controlled trial beginning in 1992-1994 testing the effect of vitamin E and low dose aspirin in the primary prevention of cancer and cardiovascular disease. Information related to health and lifestyle was collected by questionnaire at baseline and during follow-up.

Genotyping in the WGHS sample was performed using the HumanHap300 Duo "+" chips or the combination of the HumanHuman300 Duo and iSelect chips (Illumina, San Diego, CA) with the Infinium II protocol. In either case, the custom SNP content was the same; these custom SNPs were chosen without regard to minor allele frequency (MAF) to saturate candidate genes for cardiovascular disease as well as to increase coverage of SNPs with known or suspected biological function, e.g. disease association, non-synonymous changes, substitutions at splice sites, etc. For quality control, all samples were required to have successful genotyping using the BeadStudio v3.3 software (Illumina, San Diego, CA) for at least 98% of the SNPs. A subset of 23,294 individuals were identified with self-reported European ancestry that could be verified on the basis of multidimensional scaling analysis of identity by state using 1,443 ancestry informative markers in PLINK v1.06²⁹. In the final dataset of these individuals, SNPs were retained with MAF >1%, successful genotyping in 90% of the subjects, and deviations from Hardy-Weinberg equilibrium not exceeding $P=10^{-6}$ in significance. Among the final 23,294 individuals of verified European ancestry, genotypes for a total of 2,608,509 SNPs were imputed from the experimental genotypes and LD relationships implicit in the HapMap release 22 CEU samples.

Young Finns

The Young Finns study (YFS) cohort is a Finnish longitudinal population study sample on the evolution of cardiovascular risk factors from childhood to adulthood⁵⁷. The first cross-sectional study was conducted in the year 1980 in five different centres. It included 3,596 participants in the age

groups of 3, 6, 9, 12, 15, and 18, who were randomly chosen from the national population register. After the baseline in 1980 these subjects have been re-examined in 1983 and 1986 as young individuals, and in 2001, 2007 (aged 30-45 years) as older individuals. For the current analysis the latest follow-up was used. This study was carried out in accordance with the recommendations of the Declaration of Helsinki. All participants provided written informed consent and the study protocol was approved by the Ethics Committee.

Genomic DNA was extracted from peripheral blood leukocytes using a commercially available kit and Qiagen BioRobot M48 Workstation according to the manufacturer's instructions (Qiagen, Hilden, Germany). Genotyping was done for 2,556 samples using custom build Illumina Human 670k BeadChip at Wellcome Trust Sanger Institute. Genotypes were called using Illuminus clustering algorithm. 56 samples failed Sanger genotyping pipeline QC criteria (i.e., duplicated samples, heterozygosity, low call rate, or Sequenom fingerprint discrepancy). From the remaining 2,500 samples one sample failed gender check, three were removed due to low genotyping call rate (< 0.95) and 54 samples for possible relatedness ($\pi\text{-hat} > 0.2$). 11,766 SNPs were excluded based on Hardy–Weinberg equilibrium (HWE) test ($p = 10^{-6}$), 7,746 SNPs failed missingness test (call rate < 0.95) and 34,596 SNPs failed frequency test ($\text{MAF} < 0.01$). After quality control there were 2,443 samples and 546,677 genotyped SNPs available for further analysis⁵⁷. Genotype imputation was performed using IMPUTE⁵⁵ version 2.1.2 and 1000 Genomes Interim Phase I June 2011 haplotypes as reference. Palindromic A/T and C/G SNPs were removed before imputation. After filtering SNPs with low Fisher information ($\text{info} < 0.4$) and $\text{MAF} (< 0.001)$ there were 12,569,109 SNPs available.

Clinic-based studies

Finnish MA study

1,032 Finnish patients having either migraine with aura (MA) or migraine with and without aura (MA/MO) were collected nationwide from headache clinics. Each patient belongs to a multigenerational migraine family with at least three affected family members. All patients completed the validated Finnish Migraine Specific Questionnaire for Family Studies (FMSQ_{FS})¹⁹ and all fulfilled the current International Headache Society diagnostic criteria (ICHD-II¹⁵) for MA. In cases of insufficient or conflicting information, a follow-up interview was performed by telephone.

1,862 Finnish control subjects were obtained from the Health2000 study (<http://www.terveys2000.fi/julkaisut/baseline.pdf>) and 1,651 controls from the Helsinki Birth Cohort study⁵⁸.

Written informed consent was obtained from all participants, and the study was approved by the Helsinki University Central Hospital local ethics committee.

German MA study

The Kiel/Ulm sample consists of 758 German patients with MA. The patients were recruited at a single tertiary headache center in Northern Germany (Pain Clinic, Kiel), and first collected at the Universities of Bonn and Cologne. All patients were diagnosed as having MA according to the ICHD-II¹⁵ by experienced neurologists with a specialization in headache disorders, as described previously⁵⁹. The detailed migraine anamnesis was obtained either by face-to-face interviews or by telephone interviews. Interviews were standardized by using a comprehensive migraine questionnaire. All patients gave their written informed consent for participating in the study. The study was approved by the local university ethics committees.

The Munich sample consists of 239 cases with MA. The patients were recruited at the Department of Neurology at the Klinikum Großhadern of the Ludwig-Maximilians-University, Munich, Germany. Both in- and outpatients were recruited. All cases were personally examined by a headache specialist. For establishing the diagnosis of MA, cases were phenotyped with the help of a German translation of the Finnish validated headache questionnaire¹⁹. Whenever the information from the questionnaire was insufficient or conflicting, an additional telephone interview was performed. Information was thus obtained on all aspects of the ICHD-II¹⁵ criteria as well as on various other aspects (such as age at onset, prodromal symptoms, triggers, acute and prophylactic medication, family history, general past medical history, co-morbidity, place of birth). Written informed consent was obtained from all participants, and the study was approved by the local ethics committee.

German controls were obtained from the PopGen study⁶⁰ (n=661), all genotyped on the Illumina 550K platform. In addition, 444 controls were obtained from Illumina iControlDB by querying all Caucasian samples genotyped on the Illumina 550K platform on June 30th, 2008 and filtering these samples based on stratification as observed from multidimensional scaling plots of all existing German samples, and keeping only those identified as being of German descent.

German MO study

The German sample of 1,208 MO cases was recruited in Munich and Kiel and data were examined by a headache specialist at the Klinikum Großhadern of the Ludwig-Maximilians-University, Munich, and the Kiel Pain and Headache Center, Kiel. Phenotyping was based on a German translation of the

FMSQ_{FS}¹⁹. Particular emphasis was put on reliable exclusion of aura symptoms. In case of insufficient or conflicting information, an additional telephone interview was performed. Information was obtained on all aspects of the ICHD-II¹⁵ criteria as well as on other aspects (such as age at onset, prodromal symptoms, triggers, acute and prophylactic medication, family history, general past medical history, co-morbidity and place of birth).

Population-matched controls were obtained from pre-existing previously genotyped studies. German controls were available from the KORA S4/F4⁶¹ (n = 834) as well as from the GSK⁶² (n = 861), the MPIPSYKL (n = 489) and the HNR⁶³ (n = 380) studies.

LUMINA MA study

The Dutch MA GWAS contains 879 Dutch MA patients that were available from the clinic-based Leiden University Migraine Neuro Analysis (LUMINA) study. Of the 820 MA cases, 146 (18%) were male and 674 (82%) were female. Self-reported migraineurs were recruited via the project's website (www.lumc.nl/hoofdpijn). A set of previously validated screening questions was used³⁸. Participants fulfilling the screening criteria then completed an extended questionnaire that focuses on signs and symptoms of migraine headache and aura as outlined in ICHD-II¹⁵. Individual diagnoses were made using an algorithm based on these criteria and that was validated by a semi-structured telephone interview performed by experienced physicians or by well-trained medical students, when necessary in consultation with a neurologist specialized in headache (GMT)⁶⁴. A subset of the patients was asked to participate upon visiting the outpatient clinic. Population-matched controls (n=4,774) were obtained from the Rotterdam Study I⁵³.

LUMINA MO study

The Dutch MO GWAS contains 1,118 Dutch MO patients, of which 159 (14%) were male and 959 (86%) were female, that were available from the clinic-based Leiden University Migraine Neuro Analysis (LUMINA) study. Self-reported migraineurs were recruited via the project's website (www.lumc.nl/hoofdpijn). A set of screening questions validated previously in a population-based study³⁸ was used. Participants fulfilling the screening criteria then completed an extended questionnaire that focuses on signs and symptoms of migraine headache and aura (aura symptoms were absent in the selected patient group) as outlined in ICHD-II. Individual diagnoses were made using an algorithm based on these criteria, validated by a semi-structured telephone interview performed by experienced physicians or by well-trained medical students, when necessary in consultation with a neurologist specialized in headache (GMT)⁶⁴. A subset of the patients was asked to participate upon visiting the outpatient clinic. Population-matched controls (n=2,016) were obtained from the Rotterdam Study II (RSII)⁵³.

Analysis of brain eQTL data

The expression quantitative trait loci (eQTL) analysis sample was composed of 475 neurologically normal Caucasian subjects from the United States and the United Kingdom. Tissue from the cerebellum (CRBLM) and frontal cortex (FCTX) were obtained for all subjects (950 tissue samples). Genotyping was performed from the cerebellum tissue samples using the Illumina HumanHap550 v3, Human610-Quad v1, Human660W-Quad v1 and HumanOmni1-Quad v1 Infinium Beadchips. Expression profiling for mRNA transcripts was assayed using the Illumina HumanHT-12 v3 Expression Beadchip. Processing and analysis of these data were performed in a manner similar to methods previously described for studies including these subjects⁶⁵⁻⁶⁷ (GEO # GSE36192, dbGaP # phs000249).

Genotype and expression based filtering included subject and SNP filtering based on call rate, expected subject gender, relatedness among subjects, population outliers when combined with HapMap3 genotypes, if a subject was less than 15 years of age or removal of subjects if either of their tissue sample expression profiles were outliers based on mean normalized intensity profile or mean expression detection rate. After filtering 394 subjects remained; 1 subject was removed based on genotype call rate, 3 based on discrepancies between reported and genotyped gender, 1 due to relatedness, 2 as they were duplicates of each other, 10 from being population outliers, 43 based on being an expression outlier or missing expression in one or both tissues and 28 subjects were excluded based on age. Genotype based metrics for filtering was performed using the Plink toolset²⁹ and R.

A two-step imputation process was performed excluding genotyped SNPs where SNP and subject callrate were less than 95%, MAF was less than 1% and Hardy-Weinberg equilibrium (HWE) *P* values were less than 0.000001. Mach²⁸ and MiniMac⁶⁸ were used to impute genotypes for ~37.4 million autosomal SNPs based on European reference haplotypes from the 1000 Genomes Phase1 v2.20101123 data. Imputed SNPs were excluded if their MAF was less than 0.01964 or the *r*² was less than 0.3 between known and imputed genotypes resulting in ~6.8 million autosomal SNPs available for eQTL analysis. The MAF threshold of 0.01964 is an estimate of the smallest allele frequency testable in this sample series and determined from the typed SNPs (after quality control) where at least 3 minor homozygotes were present.

Prior to eQTL analysis the mRNA expression data were normalized using a cubic spline within BeadStudio. The Illumina HumanHT-12 probes were re-annotated using the ReMOAT tool⁶⁹ to identify probes that may have design issues. Filtering based on the ReMOAT quality score field resulted in 14067 of the 48803 probes being excluded from analysis. Additionally to correct for potential hybridization bias resulting from polymorphisms with the mRNA 50mer probe, probes that included a SNP, with a MAF greater than or equal to 0.01964 based on the European subjects from the 1000 Genomes Phase1 v2.20101123 data, within the 50mer design were excluded from the analysis result set. Expression probes were considered reliably detected within a sample if the Illumina Detection *P* value was ≤ 0.01. An expression probe was selected for eQTL analysis if the probe was reliably detected for 95% of the QC filtered samples within a tissue type. This resulted in 8599 CRBLM and 8696 FCTX probes available to be used for the eQTL analysis. These selected probes expression profiles were then adjusted using known covariates for subject age, gender, post-mortem interval, originating tissue bank, principal components 1 through 12 based on identity-by-state pairwise distances within the filtered subjects genotypes, and the mRNA sample preparation/hybridization batch. The expression profiles were then log₂ transformed and covariates were stepwise fitted in R against the following model:

$$Y = \beta_0 + \beta_1 X_1 + \dots + \beta_n X_n + \varepsilon$$

where $\beta_0 \dots \beta_n$ represent the continuous and categorical covariates. The residuals of this model fit for each probe were then standardized, and used as the quantitative trait for the eQTL analysis.

eQTL analysis was then performed using the standardized residuals for every selected and adjusted trait in both brain tissues using mach2qtl⁷⁰ to regress the trait with the allele dosage. For each trait analyzed only SNPs that are *cis* to the trait and passed imputation QC were considered in the analysis. In this context *cis* was defined as the region near the trait, +/- 1Mb from the mRNA transcript start or end site, or within the transcript.

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Supplementary References

1. Anttila, V. *et al.* Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. *Nat Genet* **42**, 869-73 (2010).
2. Ligthart, L. *et al.* Meta-analysis of genome-wide association for migraine in six population-based European cohorts. *Eur J Hum Genet* **19**, 901-7 (2011).
3. Chasman, D.I. *et al.* Genome-wide association study reveals three susceptibility loci for common migraine in the general population. *Nat Genet* **43**, 695-8 (2011).
4. Freilinger, T. *et al.* Genome-wide association analysis identifies susceptibility loci for migraine without aura. *Nat Genet* **44**, 777-82 (2012).
5. Schreiner, A. *et al.* Junction protein shrew-1 influences cell invasion and interacts with invasion-promoting protein CD147. *Mol Biol Cell* **18**, 1272-81 (2007).
6. Grass, G.D., Bratoeva, M. & Toole, B.P. Regulation of invadopodia formation and activity by CD147. *J Cell Sci* **125**, 777-88 (2012).
7. Lafleur, M.A., Xu, D. & Hemler, M.E. Tetraspanin proteins regulate membrane type-1 matrix metalloproteinase-dependent pericellular proteolysis. *Mol Biol Cell* **20**, 2030-40 (2009).
8. Hinck, A.P. Structural studies of the TGF-betas and their receptors - insights into evolution of the TGF-beta superfamily. *FEBS Lett* **586**, 1860-70 (2012).
9. Boucher, P. *et al.* LRP1 functions as an atheroprotective integrator of TGFbeta and PDGF signals in the vascular wall: implications for Marfan syndrome. *PLoS One* **2**, e448 (2007).
10. Rozanov, D.V., Hahn-Dantona, E., Strickland, D.K. & Strongin, A.Y. The low density lipoprotein receptor-related protein LRP is regulated by membrane type-1 matrix metalloproteinase (MT1-MMP) proteolysis in malignant cells. *J Biol Chem* **279**, 4260-8 (2004).
11. Zhang, H., Adwanikar, H., Werb, Z. & Noble-Haeusslein, L.J. Matrix metalloproteinases and neurotrauma: evolving roles in injury and reparative processes. *Neuroscientist* **16**, 156-70 (2010).
12. Castellano, J. *et al.* Hypoxia stimulates low-density lipoprotein receptor-related protein-1 expression through hypoxia-inducible factor-1alpha in human vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* **31**, 1411-20 (2011).

13. Chuikov, S., Levi, B.P., Smith, M.L. & Morrison, S.J. Prdm16 promotes stem cell maintenance in multiple tissues, partly by regulating oxidative stress. *Nat Cell Biol* **12**, 999-1006 (2010).
14. Park, S.J. *et al.* Astrocytes, but not microglia, rapidly sense H₂O₂ via STAT6 phosphorylation, resulting in cyclooxygenase-2 expression and prostaglandin release. *J Immunol* **188**, 5132-41 (2012).
15. International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* **24 Suppl 1**, 9-160 (2004).
16. Ligthart, L., Boomsma, D.I., Martin, N.G., Stubbe, J.H. & Nyholt, D.R. Migraine with aura and migraine without aura are not distinct entities: further evidence from a large Dutch population study. *Twin Res Hum Genet* **9**, 54-63 (2006).
17. Russell, M.B., Ulrich, V., Gervil, M. & Olesen, J. Migraine without aura and migraine with aura are distinct disorders. A population-based twin survey. *Headache* **42**, 332-336 (2002).
18. Magi, R., Lindgren, C.M. & Morris, A.P. Meta-analysis of sex-specific genome-wide association studies. *Genet Epidemiol* **34**, 846-53 (2010).
19. Kallela, M., Wessman, M. & Färkkilä, M. Validation of a migraine specific questionnaire for use in family studies. *Eur J Neurol* **8**, 61-66 (2001).
20. Kirchmann, M. *et al.* Validation of the deCODE Migraine Questionnaire (DMQ3) for use in genetic studies. *Eur J Neurol* **13**, 1239-44 (2006).
21. Schurks, M., Buring, J.E. & Kurth, T. Agreement of self-reported migraine with ICHD-II criteria in the Women's Health Study. *Cephalalgia* **29**, 1086-90 (2009).
22. Segre, A.V., Groop, L., Mootha, V.K., Daly, M.J. & Altshuler, D. Common inherited variation in mitochondrial genes is not enriched for associations with type 2 diabetes or related glycemic traits. *PLoS Genet* **6**(2010).
23. Rossin, E.J. *et al.* Proteins encoded in genomic regions associated with immune-mediated disease physically interact and suggest underlying biology. *PLoS Genet* **7**, e1001273 (2011).
24. Raychaudhuri, S. *et al.* Identifying relationships among genomic disease regions: predicting genes at pathogenic SNP associations and rare deletions. *PLoS Genet* **5**, e1000534 (2009).
25. Cotsapas, C. *et al.* Pervasive sharing of genetic effects in autoimmune disease. *PLoS Genet* **7**, e1002254 (2011).

26. Lage, K. *et al.* A human phenome-interactome network of protein complexes implicated in genetic disorders. *Nat Biotechnol* **25**, 309-16 (2007).
27. Fraser, A. *et al.* Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol* (2012).
28. Li, Y., Willer, C.J., Ding, J., Scheet, P. & Abecasis, G.R. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. *Genet Epidemiol* **34**, 816-34 (2010).
29. Purcell, S. *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* **81**, 559-75 (2007).
30. Medland, S.E. *et al.* Common variants in the trichohyalin gene are associated with straight hair in Europeans. *Am J Hum Genet* **85**, 750-5 (2009).
31. Power, C. & Elliott, J. Cohort profile: 1958 British birth cohort (National Child Development Study). *Int J Epidemiol* **35**, 34-41 (2006).
32. Strachan, D.P. *et al.* Lifecourse influences on health among British adults: effects of region of residence in childhood and adulthood. *Int J Epidemiol* **36**, 522-31 (2007).
33. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661-78 (2007).
34. Barrett, J.C. *et al.* Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nat Genet* **41**, 703-7 (2009).
35. Moffatt, M.F. *et al.* A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* **363**, 1211-21 (2010).
36. Aulchenko, Y.S., Struchalin, M.V. & van Duijn, C.M. ProbABEL package for genome-wide association analysis of imputed data. *BMC Bioinformatics* **11**, 134 (2010).
37. Sleegers, K. *et al.* Cerebrovascular risk factors do not contribute to genetic variance of cognitive function: the ERF study. *Neurobiol Aging* **28**, 735-41 (2007).
38. Launer, L.J., Terwindt, G.M. & Ferrari, M.D. The prevalence and characteristics of migraine in a population-based cohort: The GEM Study. *Neurology* **53**, 537-542 (1999).
39. Stam, A.H. *et al.* Shared genetic factors in migraine and depression: evidence from a genetic isolate. *Neurology* **74**, 288-94 (2010).

40. Kaprio, J., Pulkkinen, L. & Rose, R.J. Genetic and environmental factors in health-related behaviors: studies on Finnish twins and twin families. *Twin Res* **5**, 366-71 (2002).
41. Knaapila, A. *et al.* Food neophobia in young adults: genetic architecture and relation to personality, pleasantness and use frequency of foods, and body mass index--a twin study. *Behav Genet* **41**, 512-21 (2011).
42. Hagen, K., Zwart, J.A., Vatten, L., Stovner, L.J. & Bovim, G. Head-HUNT: validity and reliability of a headache questionnaire in a large population-based study in Norway. *Cephalalgia* **20**, 244-51. (2000).
43. McKay, J.D. *et al.* Lung cancer susceptibility locus at 5p15.33. *Nat Genet* **40**, 1404-6 (2008).
44. Penninx, B.W. *et al.* The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res* **17**, 121-40 (2008).
45. Boomsma, D.I. *et al.* Netherlands Twin Register: from twins to twin families. *Twin Res Hum Genet* **9**, 849-57 (2006).
46. Ligthart, L. *et al.* Migraine symptomatology and major depressive disorder. *Cephalalgia* **30**, 1073-81 (2010).
47. Boomsma, D.I. *et al.* Genome-wide association of major depression: description of samples for the GAIN Major Depressive Disorder Study: NTR and NESDA biobank projects. *Eur J Hum Genet* **16**, 335-42 (2008).
48. Marchini, J., Howie, B., Myers, S., McVean, G. & Donnelly, P. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet* **39**, 906-13 (2007).
49. Rantakallio, P. Groups at risk in low birth weight infants and perinatal mortality. *Acta Paediatr Scand* **193**, Suppl 193:1+ (1969).
50. Sovio, U. *et al.* Cloninger's Temperament dimensions, socio-economic and lifestyle factors and metabolic syndrome markers at age 31 years in the Northern Finland Birth Cohort 1966. *J Health Psychol* **12**, 371-82 (2007).
51. Sabatti, C. *et al.* Genome-wide association analysis of metabolic traits in a birth cohort from a founder population. *Nat Genet* **41**, 35-46 (2009).
52. Hofman, A. *et al.* The Rotterdam Study: objectives and design update. *Eur J Epidemiol* **22**, 819-29 (2007).
53. Hofman, A. *et al.* The Rotterdam Study: 2012 objectives and design update. *Eur J Epidemiol* **26**, 657-86 (2011).
54. Moayyeri, A., Hammond, C.J., Valdes, A.M. & Spector, T.D. Cohort Profile: TwinsUK and Healthy Ageing Twin Study. *Int J Epidemiol* (2012).

55. Howie, B.N., Donnelly, P. & Marchini, J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet* **5**, e1000529 (2009).
56. Chen, M.H. & Yang, Q. GWAf: an R package for genome-wide association analyses with family data. *Bioinformatics* **26**, 580-1 (2010).
57. Raitakari, O.T. *et al.* Cohort profile: the cardiovascular risk in Young Finns Study. *Int J Epidemiol* **37**, 1220-6 (2008).
58. Barker, D.J., Osmond, C., Forsen, T.J., Kajantie, E. & Eriksson, J.G. Trajectories of growth among children who have coronary events as adults. *N Engl J Med* **353**, 1802-9 (2005).
59. Todt, U. *et al.* Variation of the serotonin transporter gene SLC6A4 in the susceptibility to migraine with aura. *Neurology* **67**, 1707-9 (2006).
60. Krawczak, M. *et al.* PopGen: population-based recruitment of patients and controls for the analysis of complex genotype-phenotype relationships. *Community Genet* **9**, 55-61 (2006).
61. Wichmann, H.E., Gieger, C. & Illig, T. KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen* **67 Suppl 1**, S26-30 (2005).
62. Muglia, P. *et al.* Genome-wide association study of recurrent major depressive disorder in two European case-control cohorts. *Mol Psychiatry* (2008).
63. Schmermund, A. *et al.* Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL Study. Risk Factors, Evaluation of Coronary Calcium and Lifestyle. *Am Heart J* **144**, 212-8 (2002).
64. van Oosterhout, W.P. *et al.* Validation of the web-based LUMINA questionnaire for recruiting large cohorts of migraineurs. *Cephalalgia* **31**, 1359-67 (2011).
65. Gibbs, J.R. *et al.* Abundant quantitative trait loci exist for DNA methylation and gene expression in human brain. *PLoS Genet* **6**, e1000952 (2010).
66. Hernandez, D.G. *et al.* Integration of GWAS SNPs and tissue specific expression profiling reveal discrete eQTLs for human traits in blood and brain. *Neurobiol Dis* **47**, 20-8 (2012).
67. Trabzuni, D. *et al.* MAPT expression and splicing is differentially regulated by brain region: relation to genotype and implication for tauopathies. *Hum Mol Genet* **21**, 4094-103 (2012).

68. Howie, B., Fuchsberger, C., Stephens, M., Marchini, J. & Abecasis, G.R. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nat Genet* **44**, 955-9 (2012).
69. Barbosa-Morais, N.L. *et al.* A re-annotation pipeline for Illumina BeadArrays: improving the interpretation of gene expression data. *Nucleic Acids Res* **38**, e17 (2010).
70. Li, Y., Willer, C., Sanna, S. & Abecasis, G. Genotype imputation. *Annu Rev Genomics Hum Genet* **10**, 387-406 (2009).